VOL. 46 AUGUST, 1953 No. 2

AMERICAN HEART JOURNAL

AN INTERNATIONAL PUBLICATION FOR
THE STUDY OF THE CIRCULATION

Contents on Inside Cover

American Heart Journal

CONTENTS FOR AUGUST, 1953

Original Communications

Clinical Reports

Announcements

Book Reviews

Vol. 46, No. 2, August, 1953. American Heart Journal is published monthly, by The C. V. Mosby Company, 3207 Washington Avenue, St. Louis 3, Missouri, entered as second class matter January 23, 1917 at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Additional entry authorized at Jefferson City, Missouri. Subscription Price: United States, its Possessions, Pan-American Countries, $12.00; In Canada and other Foreign Countries, $13.00. Printed in the U. S. A.

American Heart Journal

VOL. 46 AUGUST, 1953 NO. 2

Original Communications

SOME LIMITATIONS OF VECTORCARDIOGRAPHY

DAVID BIBER, M.D., AND MORTIMER L. SCHWARTZ, M.D.

IRVINGTON, N. J.

THE vectorcardiogram was first proposed by Mann as a simplified version of the electrocardiogram.[1] It is simple because in any given plane one figure can be used instead of several leads. Furthermore, it is an excellent device for demonstrating the relationship of the various leads to each other. However, when vectorcardiography is compared with conventional electrocardiography its clinical value is seen to be limited. To illustrate some of these limitations the following case is cited:

R. B., a 35-year-old man, was seen in the Irvington General Hospital, Cardiovascular Clinic, Oct. 6, 1952. He stated that about four weeks previously he had had severe chest pain lasting several hours. The history was otherwise negative, and the physical findings disclosed no abnormalities. When the twelve lead electrocardiogram taken on a direct-writer was completed and viewed, it occurred to us that some of the details of the complexes of the precordial leads would not be recorded on a vectorcardiogram if the latter were taken from peripheral leads. In order to test this idea more closely a posteroanterior lead was taken immediately without changing the patient's position.

The expression "peripheral leads" refers to those leads taken at a distance from the heart. These include the limb leads and those trunk leads away from the precordial area. Precordial leads are not always peripheral; this is the primary cause of the vectorcardiographic inadequacies described here.

Lead PA, (Fig. 1), the posteroanterior lead, was a bipolar lead taken at the level of the tenth thoracic vertebra with one electrode at the right posterior axillary line and the other at the right anterior axillary line. The polarity was such that relative positivity at the anterior electrode produced an upward deflection.

From the Cardiovascular Clinic, Irvington General Hospital, Irvington, N. J.
Received for publication Feb. 7, 1953.

The frontal plane vectorcardiogram is shown in Fig. 2. The loops were constructed from Leads I and aV_F of Fig. 1 in the following manner. The amplitude of the ventricular complex in each of these leads was determined at successive intervals of 0.01 second. By plotting these values the successive instantaneous vectors were obtained and marked off on Bayley's triaxial reference system. Finally, the vectorcardiogram was constructed by drawing a smooth curve which started at the origin and passed through the distal points of the successive instantaneous vectors.

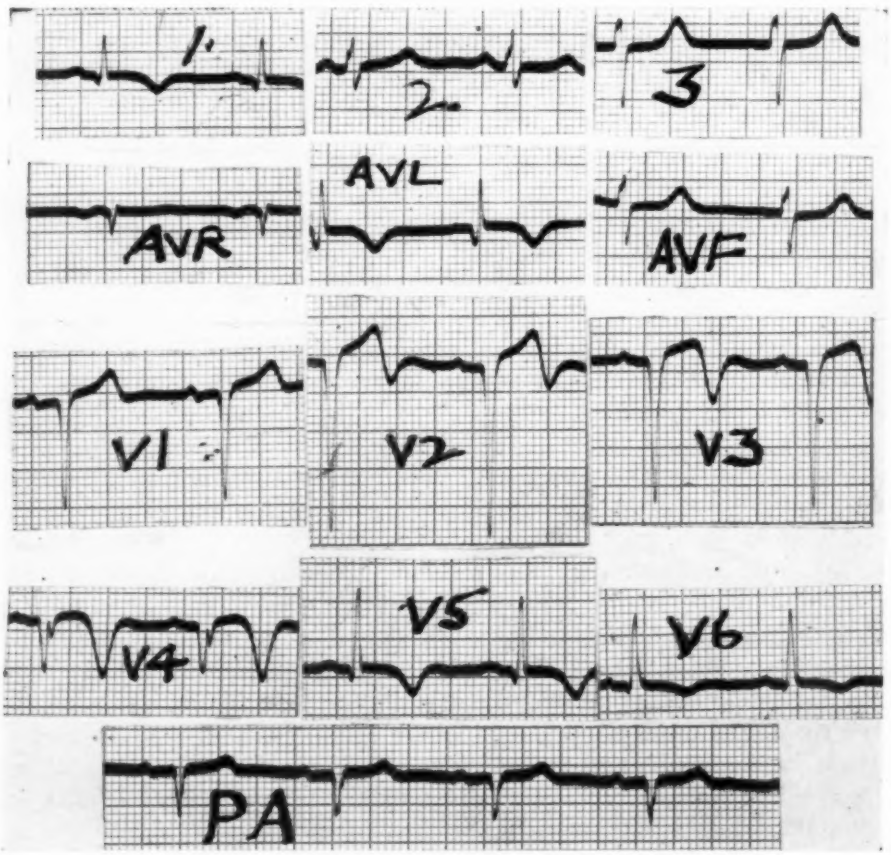

Fig. 1.—Lead PA is a posteroanterior lead taken at the level of the tenth thoracic vertebra. One electrode lies on the anterior axillary line and the other on the posterior axillary line. When the anterior electrode is relatively positive an upright complex is being inscribed.

The ventricular complexes seen in Fig. 2 were constructed from this vectorcardiogram in a manner similar to that which will be described for aV_L. An observer in Fig. 2 looking down the line of aV_L from the electrode position toward the center of the reference system views the loop as positive or negative depending upon whether or not it lies on the proximal or distal side of the line (in this case, Lead II) which is perpendicular to the lead we are deriving (in this case, aV_L). Thus, it is seen that the QRS complex of aV_L is at first slightly negative and then markedly positive; the T wave as indicated by the smaller loop is negative throughout the cycle.

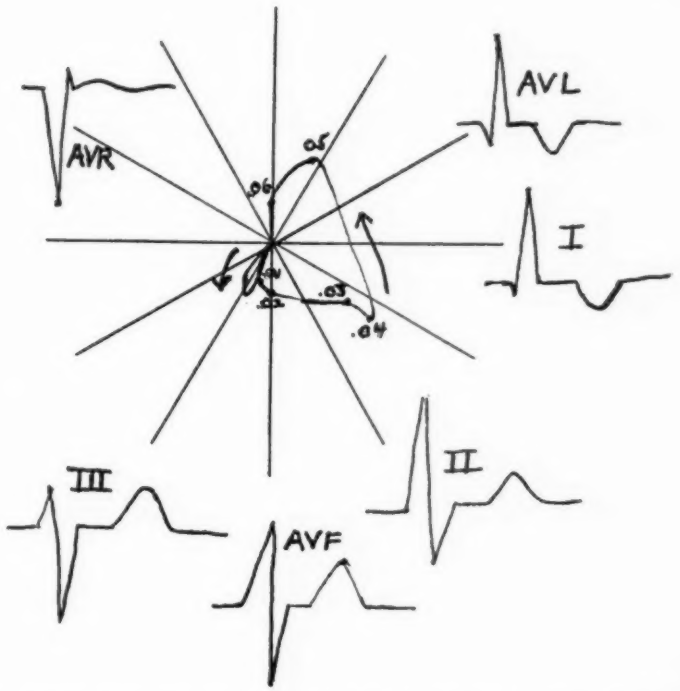

Fig. 2.—The frontal plane vectorcardiogram and the ventricular complexes derived from it. The vectorcardiogram was constructed from Leads I and aV_F of Fig. 1 as described in the text. The QRS loop is the larger. The dots on it represent the distal ends of the successive instantaneous vectors, and the numerals indicate the position in time of each of these vectors. Note that the ventricular complexes portrayed above resemble fairly closely the corresponding complexes of the electrocardiogram of Fig. 1.

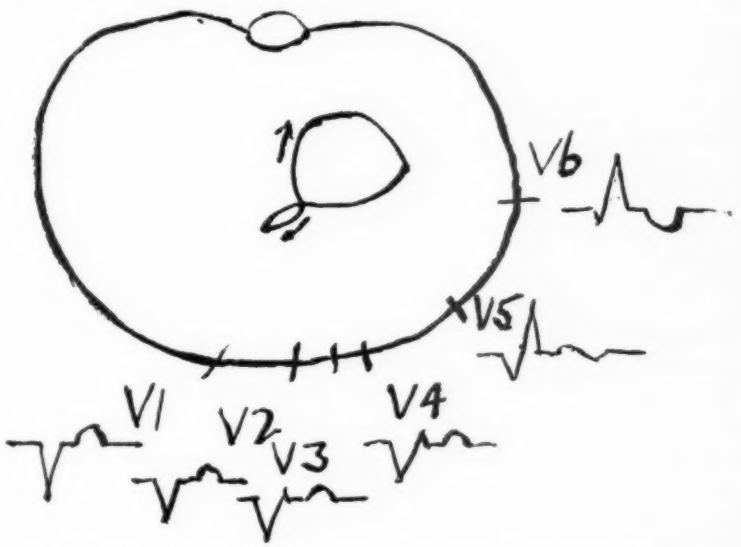

Fig. 3.—The QRS loop is the larger. Both loops have been drawn by considering Lead I and Lead PA as lying in the horizontal plane at right angles to each other. The precordial complexes have been derived from the loops. It can be seen that they differ from those taken directly as seen in Fig. 1.

The ventricular complexes obtained from the QRS loop by this method resemble fairly closely the corresponding ventricular complexes of the electrocardiogram of Fig. 1. One may conclude that in this case a vectorcardiogram derived from Leads I and aV_F can, with fair accuracy, replace the six frontal plane leads.

However, when the precordial leads are compared with the horizontal plane vectorcardiogram (Fig. 3) certain discrepancies are seen.

1. Lead PA shows a QRS duration of 0.06 second and Lead I shows a QRS duration of 0.06 to 0.07 second. Thus the QRS loop formed by the vector addition of these leads would have a duration of no more than 0.07 second. Such a loop could not indicate the fact that the QRS duration in Lead V_4 is 0.08 second.

2. The ascending limb of the QRS complex in Lead V_4 shows an embryonic R which occurs about 0.03 second before the inscription of the complex is completed. Inspection of Leads I and PA shows that a vector loop derived from them will not reflect the true contour of Lead V_4. Such a QRS loop, constructed by the vectorial addition of Lead I and Lead PA, is shown in Fig. 3. The diagram of the cross section of the thorax has been taken from another author.[2] Drawings of complexes derived from this loop are shown at their respective positions.

3. The horizontal T loop derived from Leads I and PA is shown in Fig. 3. It is seen that such a loop would give a positive T in V_1, V_2, V_3, and V_4, a diphasic T in V_5, and a negative T in V_6. Thus the electrocardiographic precordial lead T waves (Fig. 1) and the horizontal T loop do not correspond.

4. In Lead V_4 (Fig. 1) the T wave has a greater amplitude than the QRS complex. The vectorcardiogram of Fig. 3 does not reflect this relationship.

DISCUSSION

It appears that the conventional electrocardiogram of Fig. 1 gives more information than could be obtained from a spatial vectorcardiogram derived from peripheral leads. One might object to such a conclusion on the grounds that the vectorcardiogram was not taken by means of a cathode-ray vectorgraph but was estimated from the electrocardiogram. However, the discrepancies are large enough to make it obvious that they are not the result of mechanical error.

At this point it should be emphasized that under the most favorable circumstances the QRS loop of the cathode-ray vectorgram can only equal and never exceed in accuracy the QRS complexes of the electrocardiogram. This statement applies also to the P and T loops. The cathode-ray tube does no more than add two leads vectorially. It can put nothing into the loop which it does not get from the leads, and it is unreasonable to ascribe properties to the loop which are not present in the leads from which it is derived. Anything added by the cathode-ray tube must be artifact.

The discrepancies described above are not uncommon. Grant describes a case of "isolated T-wave negativity" in which a negative T wave was found at position V_4, although the T wave was upright when recorded from positions all round this area.[3] Regardless of the cause of this phenomenon it may be stated that a vectorcardiogram taken with any system of peripheral leads would fail to reveal it.

Duchosal and Grosgurin found that in eight of one hundred-two instances the horizontal QRS loop failed to correlate with conventional precordial leads.[4]

They were able to explain these failures by means of one or the other of the following hypotheses: 1. There is a single instantaneous vector the origin of which is not constant but moves during the cycle. 2. There are two or more simultaneously acting vectors which do not create a single resultant field. Here again it is seen that if the vectorcardiogram and the electrocardiogram were both taken from peripheral leads there would be good correlation between them. The discrepancy occurred because in the eight patients described above the precordial leads were not peripheral.

When peripheral leads are used it is possible to express the electrical forces of the heart as a single vector. In some individuals, however, the precordial leads are not truly peripheral so that electrical events relatively close to the electrode contribute more to the resultant potential than do more distant events. Consequently, in these circumstances the vectorcardiogram could not convey as much information as the electrocardiogram unless more than one vector were used. In connection with a discussion of intracardiac leads Kossmann and coworkers point out that the reduction of all the ventricular electromotive forces to a single vector is probably too gross for practical value.[5] Burger and van Milaan come to the same conclusion on a simple mathematical basis.[6] They state that "it is not self-evident that the electric action of the heart can be represented by one heart-vector."

Consideration of the foregoing statements makes it appear that the clinician can take a three lead electrocardiogram consisting of Leads I, aV_F, and PA, and get as much information from it as he can get from a vectorcardiogram. It also appears that in cases like the one described above, the vectorcardiogram may not prove as useful as the electrocardiogram with multiple precordial leads.

CONCLUSIONS

In some individuals the horizontal plane vectorcardiogram may fail to reflect changes which are recorded by the precordial leads of the electrocardiogram. Because of this situation the usefulness of the vectorcardiogram is limited and may not equal that of the conventional electrocardiogram.

REFERENCES

1. Mann, H.: A Method of Analyzing the Electrocardiogram, Arch. Int. Med. **25**:283, 1920.
2. Scherlis, L., Lasser, R. P., and Grishman, A.: Spatial Vectorcardiography: The Normal Vectorcardiogram. VI. Am. Heart J. **42**:235, 1951.
3. Grant, R. P., Estes, E. H., Jr., and Doyle, J. T.: Spatial Vector Electrocardiography. The Clinical Character of the S-T and T Vectors, Circulation **3**:182, 1951.
4. Duchosal, P. W., and Grosgurin, J. R.: The Spatial Vectorcardiogram Obtained by the Use of a Trihedron and Its Scalar Comparisons, Circulation **5**:237, 1952.
5. Kossmann, C. E., Berger, A. R., Rader, B., Brumlik, J., Briller, S. A., and Donnelly, J.: Intracardiac and Intravascular Potentials Resulting From Electrical Activity of the Normal Human Heart, Circulation **2**:10, 1950.
6. Burger, H. C., and van Milaan, J. B.: Heart-vector and Leads. Part III. Geometrical Representation, Brit. Heart J. **10**:229, 1948.

THE EFFECT OF SURFACE AND RECORDING TECHNIQUE ON THE DIRECT BALLISTOCARDIOGRAM

RHETT P. WALKER, M.D.,* T. J. REEVES, M.D.,**§ KATHRYN WILLIS, M.D., LYNN CHRISTIANSON, M.D., J. RUSH PIERCE, M.D., AND DONALD KAHN

BIRMINGHAM, ALA.

OF THE several methods used for the recording of ballistic waves, the Dock method has come into widest use because of its simplicity, low cost, and portability.[1,2] It has the advantage of recording directly from the body and not through some added medium such as a table. However, there are numerous pitfalls inherent in the direct method. It is important to understand whether displacement or velocity or some combination of these two is being recorded.[3] There may be error caused by variation in the frequency response of the recording instrument,[3] by the type of pickup used, or by the type of surface on which the patient lies during the recording. The latter two factors are the principal considerations of this communication.

A disturbing observation of the authors has been that a high percentage of young normal subjects have shown tracings of grossly abnormal form, as illustrated in Fig. 1, *A*. An inspection of such tracings suggested that body oscillations were distorting the pattern of the ballistocardiogram. Circulatory forces were apparently either being augmented or diminished, depending upon the phase of oscillation occurring at the time of the circulatory force. Moreover, it was noted that minor variations in recording surfaces, position of subject, and type of pickup caused significant changes in some of the deflections. The purpose of this report is to evaluate these factors.

METHODS

Surfaces.—All tracings were made in a room with a concrete floor. Varieties of substances tested included: concrete floor, heavy braced wood table, mattresses of Fiberglas, 2-inch foam rubber, and 2-inch kapok, various types of headrests and footrests, sand, and "putty." Fiberglas is a commercial heat-insulating material used in a 6-inch thickness, lying directly on the concrete floor.

From the Department of Medicine, Medical College of Alabama, Birmingham, Alabama.

This investigation was supported in part by a research grant [PHS H959 (C)] from the National Heart Institute, National Institutes of Health, Public Health Service.

Received for publication March 20, 1953.

*Public Health Research Fellow of the National Institutes of Health.

**Work done during the tenure of a National Heart Institute Traineeship, National Institutes of Health, Public Health Service.

§Beaumont, Texas.

The headrest consisted of a wood block lined with one-inch foam rubber and notched to conform to the head. The footrest consisted of a similar wood block, lined with foam rubber and notched to maintain the feet perpendicular to the table. For the studies in sand a wood box 2½ feet by 7 feet, lying on the concrete floor, was filled with 5 inches of sand and covered with an ordinary sheet. The "putty" used was a nonhardening caulking material, sold under the trade name Flexiseal, mixed with a little sand to increase its viscosity, and placed in a wood box similar to that used for the sand.

Recording Instruments.—A four-channel Cambridge Simpliscribe direct-writing instrument was used. Ballistocardiographic pickups employed were: a commercial coil-magnet capacitor system similar to that described by Dock, a bellows air-conduction system, a Sanborn photoelectric cell, and a direct crystal pickup. All of these are displacement instruments with the exception of the coil-magnet capacitor instrument, which produces a tracing that is a combination of velocity and displacement. The coils of this pickup rested at about the middle of the subject's shins, moving in relation to a fixed magnet.

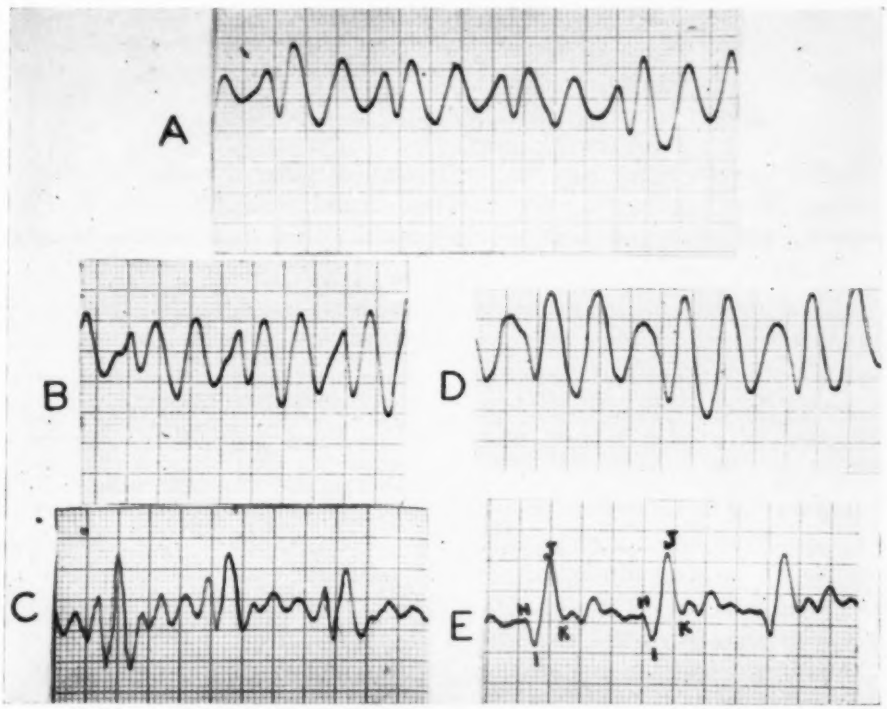

Fig. 1.—*A.* Ballistocardiogram on a 30-year-old, healthy man, made on the wooden table with a block beneath the heels and using coil-magnet with 25 microfarad capacitor. Note the marked oscillatory type pattern, almost a sine wave.

***B.* Record of a 27-year-old, healthy man on floor, using coil-magnet with 25 microfarad capacitor. No block was used under heels. Note marked oscillatory type pattern.**

***C.* Record on same subject in the sand, using coil-magnet with 25 microfarad capacitor. Note that the tracing has become essentially normal.**

***D.* Record on 25-year-old, healthy man, made on table with block beneath heels and using coil-magnet with 25 microfarad capacitor. Note marked oscillatory type pattern.**

***E.* Record on same subject in sand, using bellows displacement recording technique. Note that the record now shows a classic ballistocardiographic pattern.**

A direct crystal pickup with no filter was used as a check on the time lag and fidelity of the bellows air-conduction system. With this instrument the mechanical movements of the body were transmitted from the head by a steel rod directly to a piezoelectric crystal and relayed from there to the recording instrument. A Sanborn photoelectric cell, recording from either head or shins, was used as another check on the time lag and fidelity of the air-conduction system.

The bellows displacement apparatus, recording from the subject's head, is the same in principle as that originally described by Dock.[1] A small cylindrical metal bellows has been substituted for the glycerin capsule and the entire transducer system has been mounted in one compact unit on a lead weighted base largely protected from ambient vibration by several layers of damping material.

Calibration and Evaluation of Instruments.—A mechanical sine wave generator with a known range of motion from 0.003 to 0.024 inch and a range of frequencies from 0.8 cycle per second to 5 cycles per second was used to test the recording fidelity of the ballistocardiographic pickups. The forms of the recorded sine waves and their time relations to simultaneously recorded sine waves of the other pickups are useful in the evaluation of ballistocardiographic recording apparatus.

PROCEDURES AND RESULTS

Twelve healthy adult subjects were studied under a variety of recording conditions. Most tracings had simultaneous carotid pulses for timing, and many had velocity ballistocardiograms and electrocardiograms recorded simultaneously also.

Surfaces.—Ballistocardiograms on healthy, young adults, recorded on a flat, hard surface with the coil-magnet containing a 25 microfarad capacitor frequently showed grossly abnormal ballistocardiographic patterns. It was noted also that the form of these complexes could be altered considerably by minor changes in position such as crossing the arms and by the application of a damping force.

The first series of observations dealt with variations in recording on a wood table and on the concrete floor, in which footrests and headrests and mattresses were varied. Four healthy young adults were used as subjects. There were minor variations in wave patterns with various combinations. However, the most striking change occurred when a damping force was applied to the head of the subject. In some subjects this resulted in gross changes in the pattern of the wave, and in three of the four resulted in a marked shortening of the H-K time (Fig. 2). This led us to investigate the effect of surfaces which would have a more general damping action. Sand was selected as such a surface, because we believed that it would have a general damping action, and because it is generally available.

The second series of observations involved a comparison of a hard, flat surface and sand. As it had been observed that folding the arms would cause gross changes in the pattern in some subjects, the effect of arm folding on tracings made on the concrete floor and in the sand were studied in six healthy, normal adult subjects. Three of the subjects, whose patterns were of a grossly abnorma

oscillatory form on the floor, as illustrated in Fig. 1, *B* and 1, *D*, became essentially normal when recorded in the sand (Figs. 1, *C* and 1, *E*). Two subjects whose patterns had been comparatively normal on the floor with their arms at their sides (Fig. 3, *A*) showed a definite shortening of the J-K downstroke when they folded their arms (Fig. 3, *B*). This change did not occur in the sand with folding of the arms (Fig. 3, *C* and 3, *D*).

Because of the apparent advantage of a surface on which there is contact with the entire body from occiput to heels over a hard rigid surface, it was decided to compare sand with another similar surface, nonhardening putty. Recordings

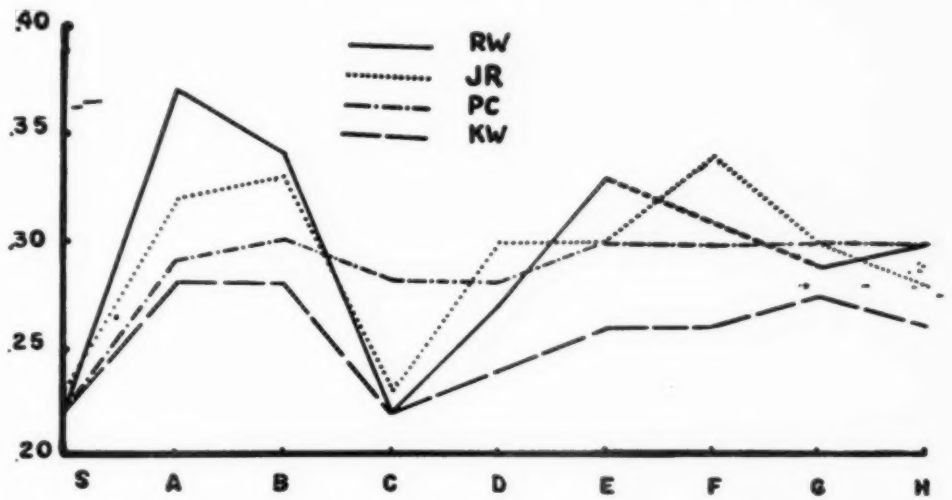

Fig. 2.—This is a graph showing changes in H-K time of four normal subjects under several conditions. Coil-magnet transducer on shins was used with 25 microfarad capacitor. Along the abscissa are plotted the various conditions. Along the ordinate is the length of the H-K time in seconds. H-K time is the time from the H peak to the K nadir. Condition *S* is in sand with arms at the side. Condition *A* is on the table with a kapok mattress and foam rubber head and footrests. Condition *B* is on the table with no mattress and with foam rubber head and footrests. Condition *C* is on the table with no mattress, with foam rubber head and footrests and with a stand against the head. Condition *D* is on the table with foam rubber headrest and with footrest without rubber, using no mattress. Condition *E* is on the table with foam rubber headrest, unnotched wooden footrest, and no mattress. Condition *F* is on the table with pillow headrest, unnotched wooden footrest, and no mattress. Condition *G* is on the table with no mattress and no head or footrests. Condition *H* is on the floor with no mattress, foam rubber head, or footrests. Note the definite shortening of the H-K time in the sand and on the table with a damping force applied as in Condition *C*. The mechanism of this shortening is probably the bringing into prominence of an early K nadir which is otherwise concealed in the downstroke following the J peak.

were made in the putty and then in the sand on four normal subjects. Study of these tracings revealed no significant difference between the two surfaces (Fig. 4). It was realized that even if putty and the sand should prove to be more satisfactory than the table or the floor for recording of the ballistocardiogram, both had definite objections as being somewhat impractical for general use. Since Fiberglas is an insulating material and has a damping effect, we thought it might be a practical material for this purpose (Fig. 5). Tracings were made also on a foam rubber mattress (Fig. 6). Both of these latter surfaces, however, produced tracings of a definite oscillatory pattern, and these surfaces were discarded.

Because of the interesting changes observed in the living subjects with changes in recording surface, it was decided to study the vibratory motion of the body in the absence of circulatory forces. Three cadavers were studied on the various surfaces. To impart motion to the cadavers a standard pendulum was used, as described by Reeves and associates.[4] This consisted of a pendulum arm, 18 inches long, suspended by means of roller bearings at the top and with a rubber handball on the bottom. This was released by an electromagnetic mechanism

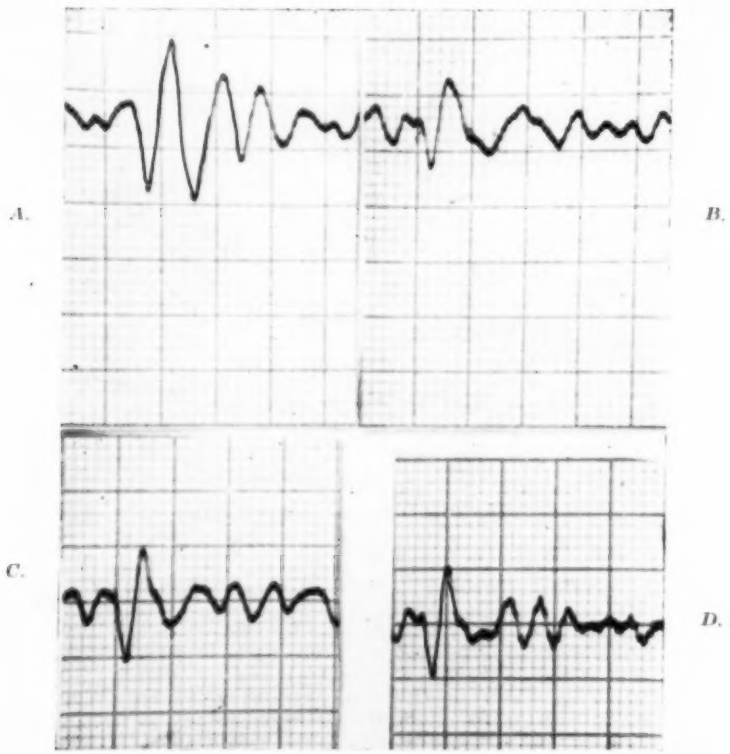

Fig. 3.—Ballistocardiogram recorded on a 52-year-old, healthy man using a coil-magnet and a 25 microfarad capacitor. *A* is a tracing made on the floor with arms at side. *B* is a tracing made on the floor with arms crossed. *C* is made in the sand with the arms at the side. *D* is made in the sand with the arms crossed. Note the definite shortening of the J-K downstroke in *B* as compared to *A* and the absence of this shortening in *D* as compared with *C*. Thus the position of the arms altered the record on the floor but had no significant effect when the subject was lying in the sand.

and allowed to fall through an arc of 45 degrees, striking a standard blow to the subject or cadaver. Several of these tracings are shown in Fig. 7. It can be seen from this cadaver study that the sand and putty had a damping action which shortened the length of time required for the oscillations to return to the base line. In one cadaver the vibratory frequency of the body was raised from about 6 to about 9 cycles per second. In another cadaver the body frequency was about fifteen on all surfaces. In the third cadaver, which was very obese, the vibratory frequency was raised from 2.5 to 4.2. The damping effect and, perhaps in some subjects at least, the elevation of vibratory frequency of the body tended to prevent the gross distortion of the ballistocardiogram which is caused frequently by

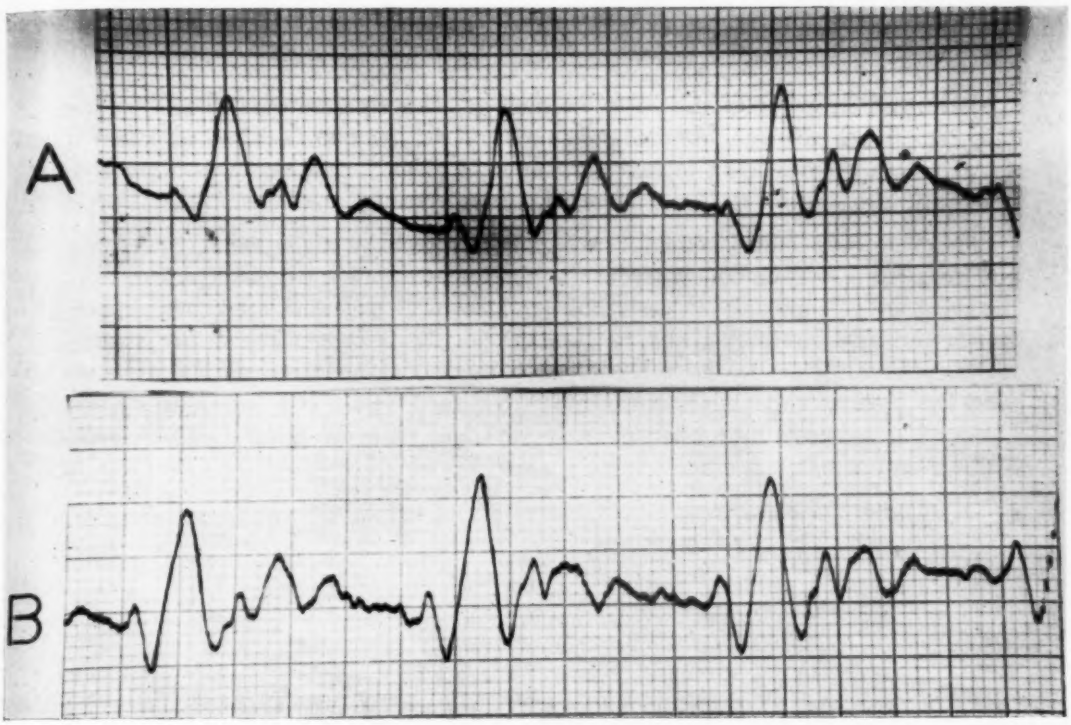

Fig. 4.—Ballistocardiogram on a 25-year-old, healthy man, made with the bellows system. *A* was made in putty; *B* was made in sand. Note that there is very little difference in the tracings.

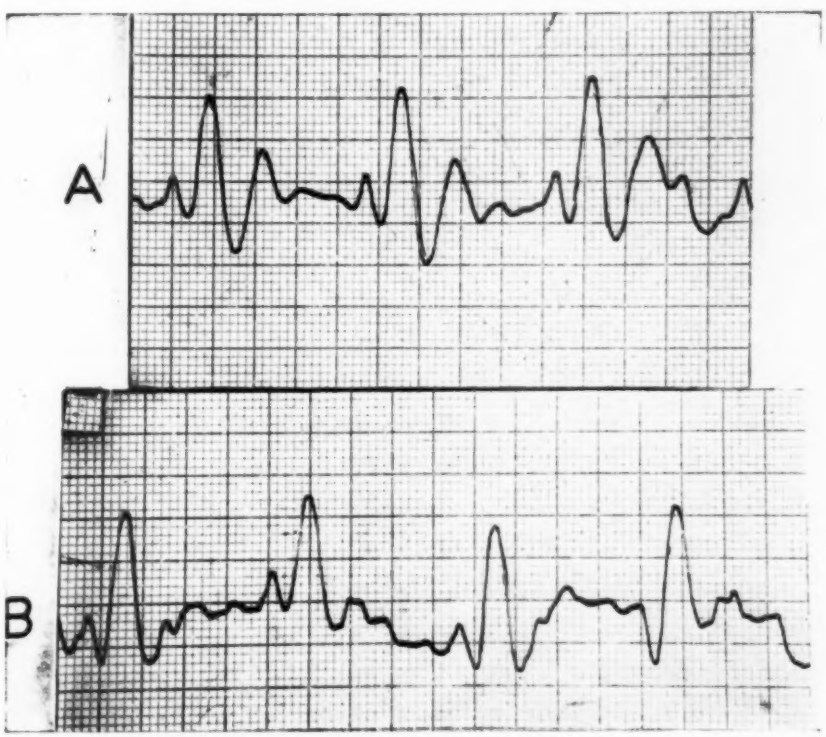

Fig. 5.—Ballistocardiogram made on a 25-year-old man, using the bellows system. *A* is a tracing made with the subject on Fiberglas. Note the tendency toward an oscillatory pattern and loss of detail on the Fiberglas, as compared to the sand, *B*.

oscillation of the body at its natural frequency. It is realized that this might not hold true in all subjects, but we have encountered only one subject in whom it did not hold. He was 76 inches tall, weighed 320 pounds, and was supported largely by the sides of the box, rather than the sand.

Instruments.—Displacement tracings which we have made, using the photocell from the head, the bellows from the head, and the direct crystal pickup from the head are so similar in pattern and in timing that we considered these instruments virtually interchangeable. Since the bellows is the easiest to use, from a technical standpoint, we have employed it most often. In our earlier work we used the glycerin capsule pickup, as described by Dock.[1] It is reasonably satisfactory but seems to be subject to more variables than the other methods, especially if any attempt is made to study wave-ratios.

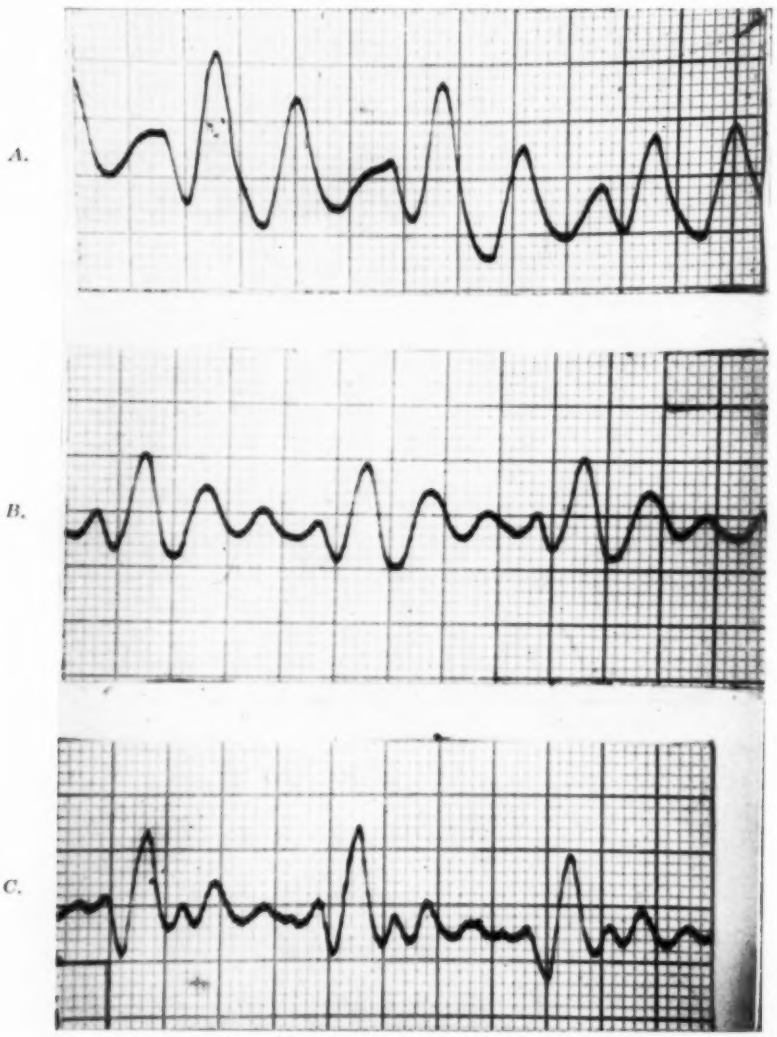

Fig. 6.—Ballistocardiogram made with the bellows system on a 26-year-old healthy man. Condition *A* is on a foam rubber mattress on the concrete floor. Condition *B* is directly on the concrete floor. Condition *C* is in the sand. Note the transition from the gross oscillatory pattern to the normal ballistocardiogram.

The coil-magnet with the 25 microfarad capacitor recording from the shins (Fig. 8, *A*) usually showed tracings which were grossly similar to those recorded by other methods from the head. In general, there is less detail and several of the smaller waves are lost. Although the causes and significance of these waves are not understood, we nevertheless believe that they should be retained until their genesis is clear.

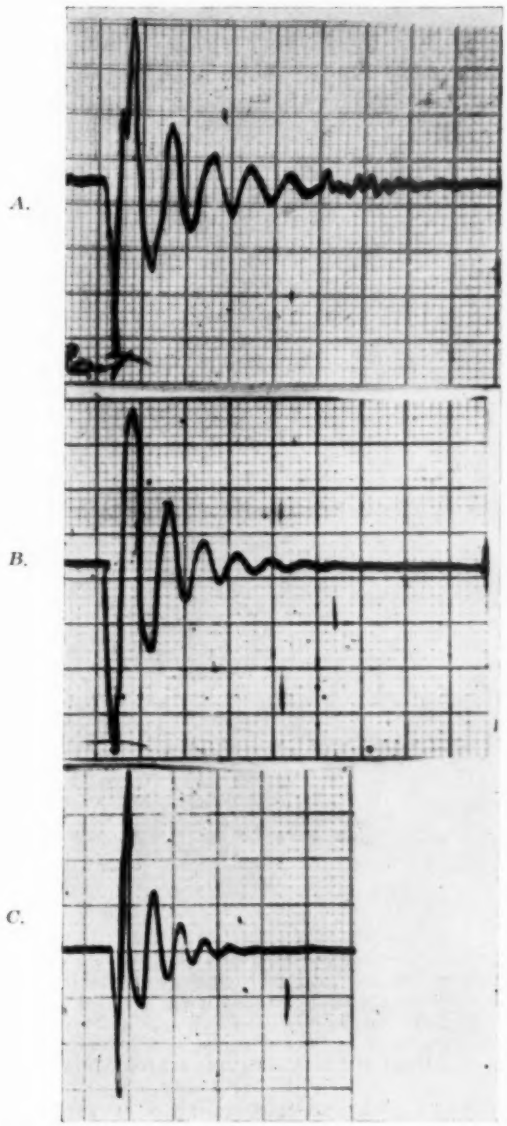

Fig. 7.—Tracings of cadaver movements following a standard pendulum tap. Coil-magnet on shins with 25 microfarad capacitor was used in these tracings. *A*, recording on the table. No heel block was used. Note the notching of the deflections and the long period required for return to the base line which occurs. Note that the vibratory frequency is about 5.5 cycles per second. *B*, on concrete floor. Note the vibratory frequency of about 5.9 cycles per second. Return to the base line required about 1.0 second. *C*, record in the sand. Note the more rapid return to the base line in 0.6 second. Note the increased vibratory frequency of about 9.1 cycles per second.

With the use of the mechanical sine wave generator, simultaneous recordings with the bellows air-conduction system (Fig. 9, *A*), the pure velocity coil-magnet (Fig. 9, *B*), and the coil-magnet with the 25 microfarad capacitor (Fig. 9, *C*) show certain interesting relations. The pure velocity tracing leads the other tracings. Theoretically, true displacement is the integral of pure velocity and should follow it by 90 degrees. The sine wave produced with the bellows air-conduction system lags approximately 90 degrees behind the pure velocity tracing, which would indicate that the bellows yields an almost pure displacement tracing. The coil-magnet with the 25 microfarad capacitor lags pure velocity by approximately 45 degrees. Thus this tracing is neither velocity nor displacement but a mixture of both.

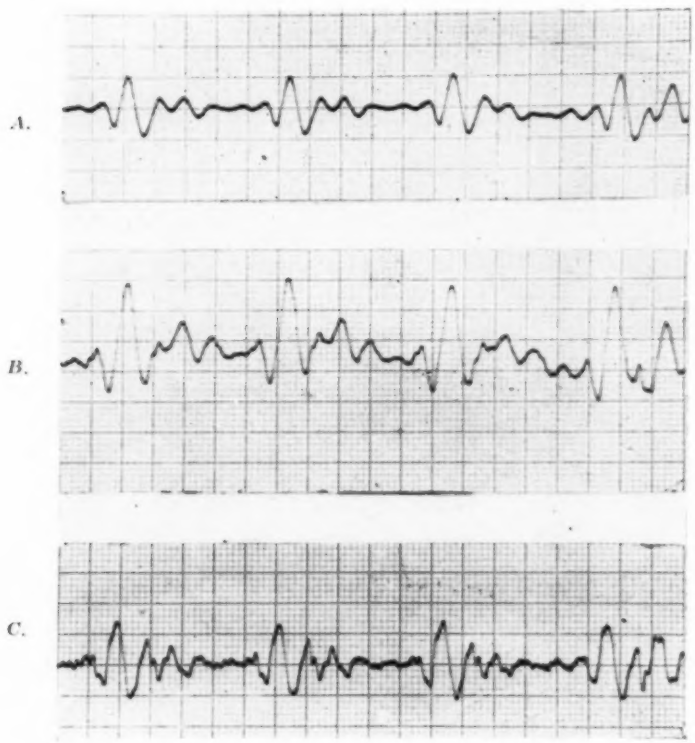

Fig. 8.—Ballistocardiograms made simultaneously on a 25-year-old healthy man, with the subject lying in the sand. *A*, record was made with coil-magnet with 25 microfarad capacitor. *B*, recorded with the bellows. *C*, recorded with a velocity pickup. Notice the greater detail in the tracing made with the bellows. Note the small notch which appears in the upstroke following the K. This is present in the bellows tracing but absent in the tracing made with the coil-magnet from the shins. Notice also the greater detail with which the diastolic waves are reproduced by the bellows.

Simultaneous recordings with the bellows (Fig. 9, *D*), pure velocity pickup (Fig. 9, *E*), and the coil-magnet with 250 microfarad filter (Fig. 9, *F*) show somewhat similar relationship. Even with this very large capacitance there is only about a 75 degree lag behind velocity. This approaches complete integration of the velocity sine wave. With the specific magnet coil and recording apparatus we have used, such a large capacitance would appear to integrate satisfactorily a velocity ballistocardiogram to a displacement ballistocardiogram.

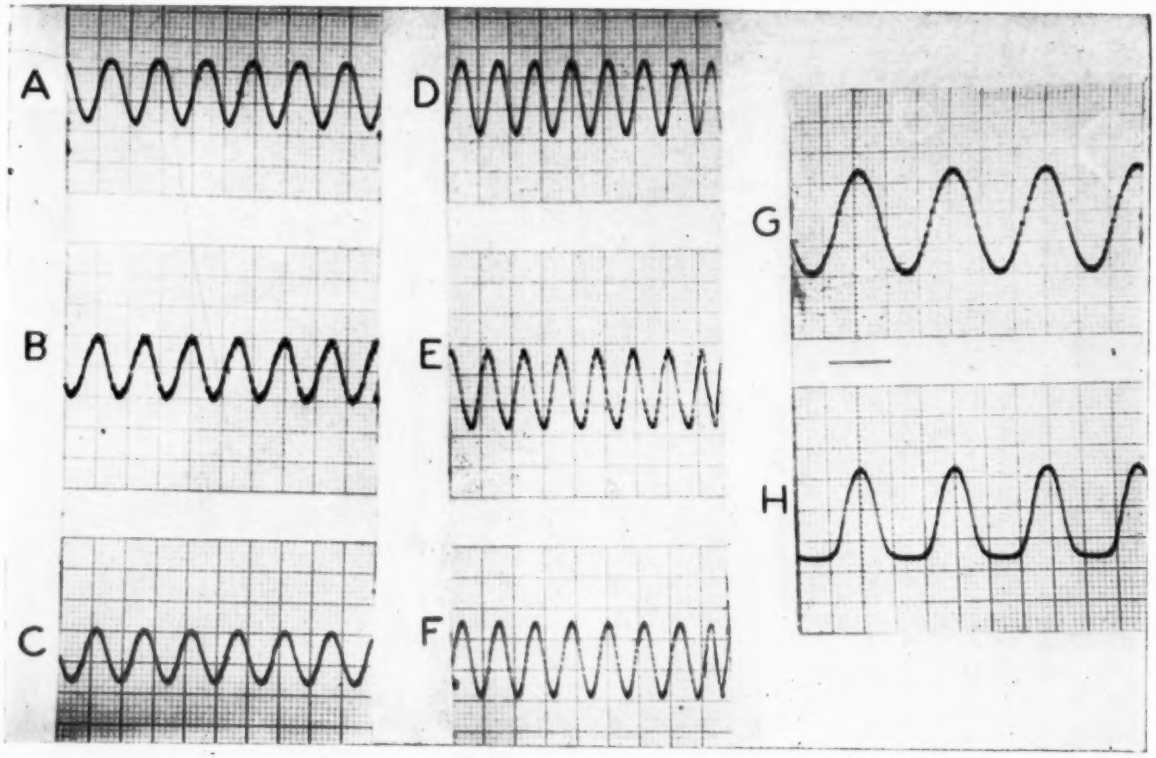

Fig. 9.—These tracings were made by recording simultaneously with various types of transducers the sine wave produced by the mechanical motion of an apparatus which moves a bar back and forth through a known range of motion. In these tracings the magnitude of the movement was 0.005 inch. The frequency of the sine wave was about three cycles per second. *A*, *B*, and *C* were made simultaneously. *A*, bellows air-conduction system. Note that this lags approximately 90 degrees behind the pure velocity tracing. *B*, record made with pure velocity technique, using a coil-magnet with no filter. Note that this leads the other tracings. *C*, coil-magnet with 25 microfarad capacitor. Note that this lags pure velocity only about 45 degrees. Thus this tracing is neither velocity nor displacement, but a mixture of each. *D*, *E*, and *F* were made simultaneously. *D*, record with bellows. Note again that this lags about 90 degrees behind pure velocity. *E*, pure velocity. *F*, coil-magnet with 250 microfarad filter. Note here that even with this very large capacitor there is still only about 75 degrees lag behind velocity. *G* and *H* were made simultaneously. *G* is the sine wave as reproduced by the bellows. *H* is the sine wave as reproduced by the gelatin capsule. Note the flattening of the bottom of the curve made with the gelatin capsule.

Simultaneous tracings made with the bellows (Fig. 9, *G*) and the gelatin capsule (Fig. 9, *H*) show a flattening of the sine wave recorded with the gelatin capsule. This is evidence that the limits of linearity in the gelatin capsule may be exceeded, even within the physiologic limits of body motion.

DISCUSSION

Surfaces.—We have abandoned using the table or any other hard, rigid surface for the recording of the direct ballistocardiogram, for the following reasons:

1. Many healthy young normal subjects showed grossly abnormal patterns on the table. These patterns become normal in putty or sand. The explanation of the abnormality of these patterns on the table is probably as follows: The vibratory frequency of the body is close enough to the frequency of the events of the cardiac cycle so that certain of the waves caused by circulatory events are augmented by body oscillations, resulting in a pattern which in some cases approaches a sine wave. Any damping force applied, such as the pressure of a wood or metal stand against the head, will produce a more nearly normal pattern. However, when the subject is lying in the putty or the sand, and damping is achieved uniformly over his body in a manner which is comparable from one individual to another, the vibratory oscillations are damped and the vibratory frequency of the body may be raised to make the natural vibrations asynchronous with the circulatory events and thus prevent the oscillatory type pattern.

2. In some subjects there is a shortening of the J-K downstroke on the table when the arms are crossed. This is not true in sand or putty. We have interpreted this to mean that on a hard surface the points of suspension of the body are changed when the subject crosses his arms. This produces a change in the ballistocardiographic pattern. In the sand or putty, since there is uniform contact, the points of suspension are changed little by changes in position, or by individual variations in body build.

3. The cadaver studies would indicate that there is a quicker return to the base line after any motion is imparted to the body lying on sand or putty. This is probably a desirable feature, in that it prevents or helps prevent resonance being set up between circulatory events and the natural frequency of the body.

4. Minor changes in footrest, headrest, mattress, etc., seem to cause relatively minor changes in the ballistocardiogram on the table, but even these minor changes might be of pathologic significance in abnormal subjects. In the sand or putty no headrest, footrest, or other support is needed.

5. Another type of evidence, which is in favor of these suggested modifications of surface and instruments, is the fact that there seems to be closer correspondence between physiologic events (recorded by the electrokymograph, heart sounds, carotid pulse, precordial tracings and jugular tracings), and the ballistocardiogram as recorded in the sand with our modified techniques. This will be discussed in more detail in a future publication.

We do not have evidence showing superiority of either the sand or the putty over one another. The sand is more practical and cheaper, but it is necessary to pack the sand around the subject each time. The putty is more comfortable and molds to the surface of the body better but tends to harden slightly with time and to vary in viscosity with changes in temperature. At present we are using the sand for most of our work, although we believe that records from the two surfaces are interchangeable. It is probable that some similar nonelastic damping surface which is superior to either will be developed. Sandbagging the patient on the floor or table does not seem feasible, as we have made unsatisfactory recordings by this method. Sandbagging the patient on a mattress has not yet been completely evaluated.

It is realized that changing from a hard flat surface to sand or similar surface may not be helpful if tracings are used purely for empirical analysis. We believe, however, that ballistocardiograms recorded from a nonelastic surface, which conforms to the contour of the body, have a closer relationship to physiologic events. Our own cadaver studies show that even with a damping surface, there are afterwaves which obviously play a role in the ballistocardiogram. If a great enough damping force is applied to completely damp out these after waves, significant physiologic waves may be, and probably are, lost. Therefore, it is realized that the sand is subject to certain artifacts which prevent it from being a perfect or even highly desirable surface. Also on many subjects it is, of course, possible to make quite satisfactory tracings on a rigid, flat surface.

Transducer.—It has not been the purpose of this paper to evaluate in detail the various types of transducers. However, in the course of our studies of surfaces certain facts have come to our attention. The coil-magnet system with the 25 microfarad capacitor across the leads was designed to give a displacement-like tracing from a velocity pickup. The effect of a large capacitor is to cause a voltage lag which may approach 90 degrees and approximate the time relations of the displacement curve. However, to yield a displacement curve from the velocity curve, a larger capacitor than 25 microfarad is necessary to produce complete integration, unless other modifications are made in the circuit (Fig. 9).

We have used the Sanborn photoelectric cell, recording both from the shins and from the head. In some subjects there seems to be a considerable difference between the recording from the shins and the recording from the head, principally in the fact that the head recording shows a shorter J-K than most other tracings reported in the literature. This may be due in part to the recording surface used. However, our recordings from the shins showed a deeper J-K downstroke. It, therefore, seemed likely that this might be the result of the rebound of the instrument on the loose skin of the shins. Dock recognized several years ago that the J-K downstroke from the head is often shorter than that recorded from the shins. He postulated that this shortening might be caused by failure of the head to follow the footward thrust of the body at that time. He also noted that tracings

from the head were distorted by kyphosis. For this reason he abandoned recording from the head in favor of the shins.[5] If sound biophysical principles of energy transfer from the body to the transducer are considered in the design of instruments, the shins may offer certain advantages over the head. These principles have been studied in detail by Smith and Bryan.[6]

SUMMARY AND CONCLUSIONS

The effect of various surfaces on the direct ballistocardiogram has been studied. It was found that hard, flat surfaces for the recording of ballistocardiograms are less desirable than a surface of a relatively nonelastic material which fits the contour of the body because of the following evidence:

1. In certain healthy, young men, grossly abnormal patterns have been observed on the table and on the floor. These patterns become normal with the subject in sand or putty.

2. Alterations of the position of the arms, with consequent alteration in the area of contact between the back and the table, may cause well-marked changes in the ballistocardiographic tracings. This change was not observed in sand or putty. We have interpreted this to mean that the points of suspension on a hard surface are important in determining the pattern of the ballistocardiogram, and that these points of suspension are not important on a surface which conforms to the contour of the body.

3. Cadaver experiments have shown a quicker return of body oscillations to the base line, following a standard tap, with an increased vibratory frequency—in some cadavers at least—in the sand and putty as compared to the table and floor.

4. Minor changes in footrest, headrest, etc., caused changes in tracings made on the table. Since no headrest or footrest was required when using putty or sand, these changes do not occur.

Neither sand nor putty is a perfect surface because after-vibrations do occur when a cadaver lying on these surfaces is set into motion. However, the duration and magnitude of these artifacts—after-vibrations—are decidedly less on these soft surfaces than on rigid surfaces. The extent to which the surface used may lead to practical errors in deciding whether or not a record is abnormal remains to be determined by future studies. In this study emphasis has been on a procedure which will be more readily adaptable for correlation with physiologic events rather than on a practical clinical procedure.

During the course of study of surfaces, we have made certain observations concerning the various types of transducers. The commercial coil-magnet system using a 25 microfarad capacitor records a mixture of velocity and displacement. If physiologic correlation is sought, this may not be desirable. Of the various types of recording apparatus we have used, a bellows with air-conduction system to a piezoelectric crystal has appeared to be quite satisfactory. The question of whether the shins or the head is the preferable site from which to record is unsettled. It is quite possible that the shins will in the course of experience prove to be superior.

The sine wave generator, the bellows pickup, and the velocity pickup were built by the Turkey Creek Manufacturing Company. Appreciation is expressed to Mr. C. F. von Herman, Jr., the owner, for his close cooperation with us. We are indebted also to Mr. Albert Thomas of Southern Research Institute for valuable technical advice.

Appreciation is also expressed to Dr. William Dock for his thoughtful and helpful criticisms.

REFERENCES

1. Dock, W., and Taubman, F.: Some Techniques for Recording the Ballistocardiogram Directly From the Body, Am. J. Med. **7**:751, 1949.
2. Dock, W., and Mandelbaum, R. A.: Ballistocardiography in Medical Practice, J.A.M.A. **146**:1264, 1951.
3. Smith, J. E., and Brown, S.: Studies of Frequency Response in Ballistocardiography. (In press.)
4. Reeves, T. J., Willis, K., Booth, E., and Ellison, Haskell: Calibration of the Direct Ballistocardiogram, Circulation **7**:732, 1953.
5. Dock, W.: Personal communication.
6. Smith, J. E., and Bryan, Samuel: Simultaneous Calibrated Recording of Displacement, Velocity, and Acceleration in Ballistocardiography, Am. Heart J. **45**:715, 1953.

THE BALLISTOCARDIOGRAM IN PERIPHERAL VASCULAR DISEASE

ARTHUR M. MASTER, M.D., EFRAIM DONOSO, M.D.,* LEON PORDY, M.D., AND KENNETH CHESKY, M.D.

NEW YORK, N. Y.

BECAUSE of the recent revival of ballistocardiography as an aid in cardiac diagnosis, it is important to discover the abnormal factors in the cardiovascular tree, which may produce abnormal patterns in the ballistocardiogram. We have, therefore, investigated the effect of peripheral vascular disease on the ballistocardiogram in patients who had no primary cardiac disease. Any alterations found in the tracings of such patients could reasonably be related to the peripheral vascular tree, rather than to the heart itself.

METHOD

The direct body type of apparatus, as described by Dock and Taubman[1] and modified by Pordy and associates,[2] was employed. In many instances, this dual apparatus[2] was used for recording both photoelectric (displacement) and electromagnetic (velocity) ballistocardiograms, simultaneously or successively. Tracings were taken during quiet respiration and on deep inspiration and expiration.[3]

In the interpretation of the ballistocardiograms, only the qualitative appearance of the component waves was considered—their amplitude, slurring, notching, or other abnormalities.[4-10]

We examined, consecutively, a group of sixty-five unselected patients from the Peripheral Vascular Disease Clinic. The diagnoses are presented in Table I.

For the purpose of this report, the patients were divided into two groups: (1) those under 50 years of age—thirty-nine cases; (2) those 50 years of age and over—twenty-six cases.

I. *Patients under 50 years of age.*—The thirty-nine cases in this group were subdivided:

1. Thirty-six patients with uncomplicated peripheral vascular disease
   a. Twenty-two with arteriosclerotic peripheral vascular disease
   b. Fourteen with thromboangiitis obliterans
2. Three cases complicated by hypertension and/or coronary disease
   a. One patient with arteriosclerotic peripheral vascular disease and coronary occlusion
   b. Two patients with thromboangiitis obliterans; one with anginal syndrome and one with coronary occlusion.

From the Cardiographic Laboratory, The Mount Sinai Hospital, New York.
Received for publication March 23, 1953.
*Fellow, John Simon Guggenheim Memorial Foundation.

TABLE I. DIAGNOSIS

Uncomplicated Arteriosclerotic P.V.D.*	22
Uncomplicated T.A.O.†	14
Arteriosclerotic P.V.D. and Hypertension	20
Arteriosclerotic P.V.D. and Coronary Occlusion	4
T.A.O. and Hypertension	3
T.A.O. and Coronary Occlusion	1
T.A.O. and Anginal Syndrome	1
Total	65

*Peripheral vascular disease
†Thromboangiitis obliterans

RESULTS

1. a. *Uncomplicated arteriosclerotic peripheral vascular disease.*—This group consisted of twenty-two patients, fourteen men and eight women, ranging in age from 35 to 49 years. All were asymptomatic from a cardiac standpoint and presented normal findings on physical examination. The blood pressure, cardiac fluoroscopy, and 12-lead resting electrocardiogram were normal. Since the presence of the peripheral vascular disease precluded the performance of the "Two-step" exercise test, we were especially careful before we decided that the patients in this group had no heart disease. The negative cardiac histories and the repeated normal physical examinations, chest fluoroscopies, and electrocardiograms supported our decision that all, or nearly all these patients, were free from cardiac disease.

TABLE II. UNCOMPLICATED P.V.D. AND RESTING BALLISTOCARDIOGRAM

DIAGNOSIS	(PATIENTS UNDER 50 YEARS)			
	TOTAL	NORMAL	ABNORMAL	BORDERLINE
Uncomplicated Arteriosclerotic P.V.D.*	22	2	18	2
Uncomplicated T.A.O.†	14	3	10	1
Total	36	5	28	3

*Peripheral vascular disease
†Thromboangiitis obliterans

Ballistocardiogram: The resting ballistocardiographic tracings were abnormal in eighteen of the twenty-two subjects (Table II), normal in two subjects, and borderline in the two others. The abnormalities most frequently encountered were tiny I waves in seven cases, and a combination of very small or absent I waves and deep K waves in six cases. Absent I waves occurred in three cases, notching of the J-K waves in one case, and deep K waves alone in one case. In summary, of the twenty-two patients under 50 years of age, with uncomplicated arteriosclerotic peripheral vascular disease, only two were found to have a completely normal ballistocardiogram at rest. Figure 1 is representative of this group. This is the ballistocardiogram of a 48-year-old man with arteriosclerotic peripheral vascular disease but with no symptoms or signs of heart disease. The electrocardiogram was normal but the ballistocardiogram was abnormal. The photoelectric tracing shows absent I wave, deeply notched upstroke of J wave and deep K wave. The electromagnetic record displays a very bizarre pattern with undetermined H wave, tiny I and J waves, and prominent K wave.

1. b. *Uncomplicated thromboangiitis obliterans.*—This group comprised fourteen patients, twelve men and two women, ranging in age from 23 to 49 years. The diagnosis of thromboangiitis obliterans was substantiated at the Peripheral Vascular Disease Clinic. Physical examination, blood pressure, cardiac fluoroscopy, and 12-lead resting electrocardiogram were normal.

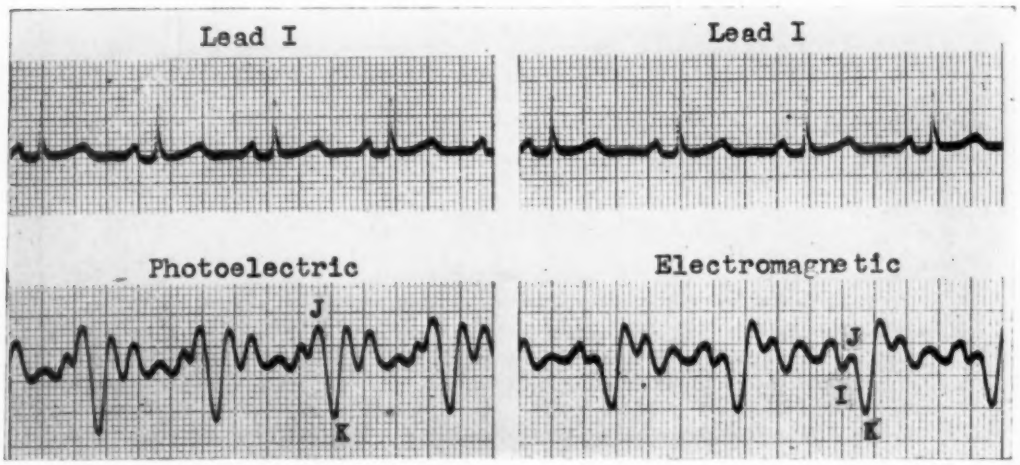

Fig. 1.—J.R., man, 48 years. Arteriosclerotic peripheral vascular disease. No cardiac symptoms; B.P. 140/80 mm. Hg; electrocardiogram normal. Ballistocardiogram abnormal: photoelectric tracing shows absent I wave, deeply notched upstroke of J wave and deep K wave. The electromagnetic record displays a very bizarre pattern with undetermined H wave, tiny *I* and *J* waves, and prominent *K* wave.

Ballistocardiogram: The resting ballistocardiograms were abnormal in ten of the fourteen patients, and normal in three patients (Table II). In one case, the tracing was borderline. The abnormalities encountered were tiny I waves and deep K waves in two cases, notched I-J waves in one case, early "M" shaped patterns in two cases, tiny I waves in four cases, and absent I waves in one case. Figure 2 illustrates a normal ballistocardiogram, both photoelectric (displacement) and electromagnetic (velocity) in a patient with uncomplicated thromboangiitis obliterans, and Fig. 3 is the abnormal ballistocardiogram of a 29-year-old white woman with thromboangiitis obliterans and normal cardiac findings.

2. a. *Complicated arteriosclerotic peripheral vascular disease* (1 case).—Among the thirty-nine patients who were under 50, only one 46-year-old woman suffered from peripheral vascular disease and coronary occlusion. The electrocardiographic tracing showed previous anterior myocardial infarction.

Ballistocardiogram (Table III): The resting ballistocardiogram was abnormal; small I waves were present.

TABLE III. COMPLICATED P.V.D. AND RESTING BALLISTOCARDIOGRAM

DIAGNOSIS	(PATIENTS UNDER 50 YEARS)			
	TOTAL	NORMAL	ABNORMAL	BORDERLINE
Arteriosclerotic P.V.D.* and Coronary Occlusion	1	0	1	0
Complicated T.A.O.†	2	0	2	0
Total	3	0	3	0

*Peripheral vascular disease
†Thromboangiitis obliterans

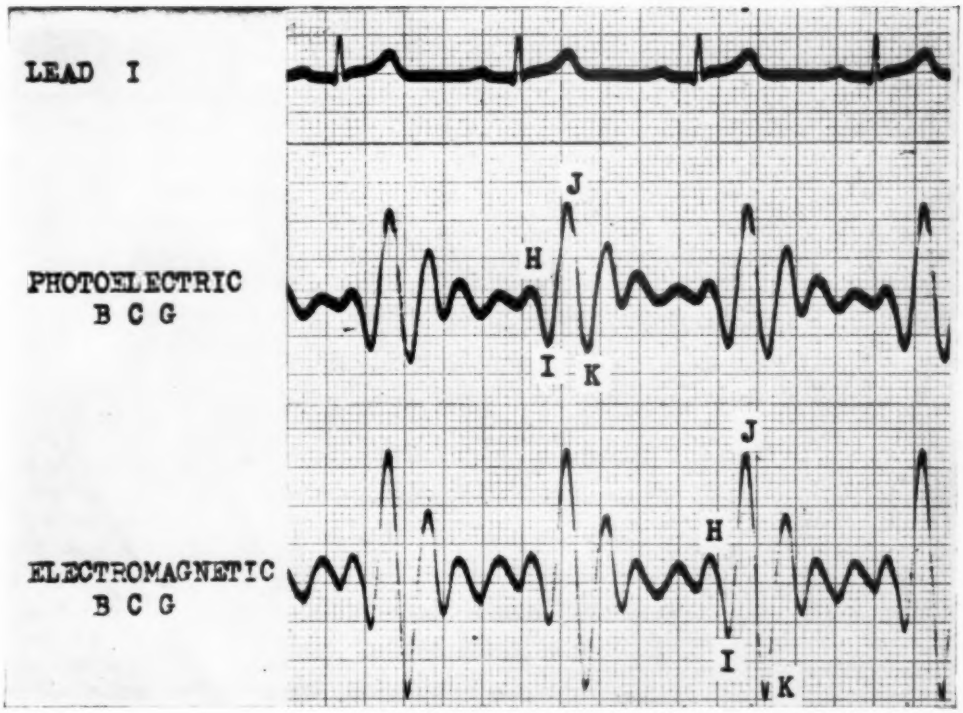

Fig. 2.—A.F., man, 31 years. Thromboangiitis obliterans, 2 years. No cardiac symptoms; B.P. 120/80 mm. Hg; electrocardiogram normal. Ballistocardiogram normal. Note that in comparison with the amplitude of the *J* and *K* waves, the *I* wave is relatively smaller in the electromagnetic tracing record as compared with the photoelectric tracing.

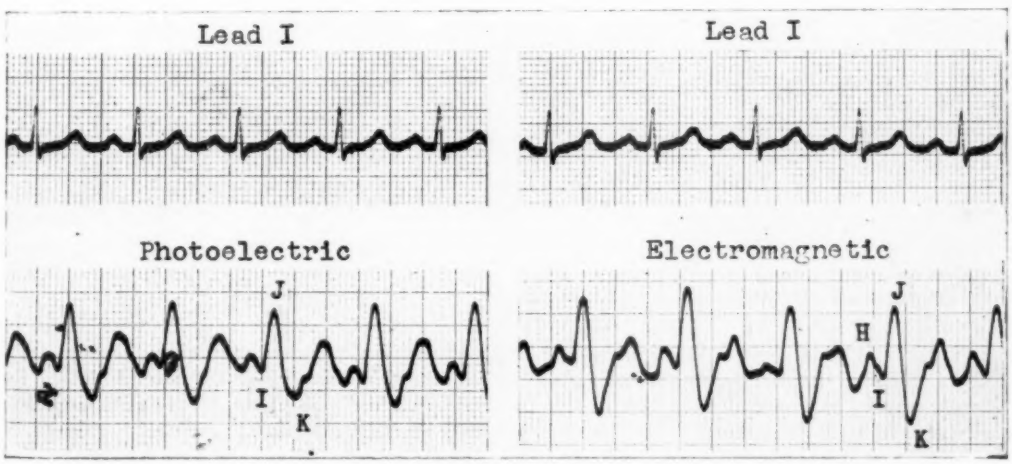

Fig. 3.—C.M., woman, 29 years. Thromboangiitis obliterans, 4 years. No cardiac symptoms; B.P. 130/80 mm. Hg; electrocardiogram normal. Ballistocardiogram abnormal; photoelectric tracing shows tiny *I* and wide *K* wave. The electromagnetic record displays alternating tiny *I*, and deeper *K* waves (note alternation in depth of the *I* waves in successive ballistocardiographic complexes).

2. b. *Complicated thromboangiitis obliterans* (2 cases).—In one case, the thromboangiitis obliterans was complicated by an anginal syndrome and, in the others, by a previous myocardial infarction.

Ballistocardiogram (Table III): The resting ballistocardiographic tracings in both patients were abnormal. There were small I waves in one case and a bizarre tracing in the other.

II. *Patients over 50 years of age* (26 cases).—These patients fell into three groups:

1. Twenty cases of arteriosclerotic peripheral vascular disease and hypertension
2. Three cases of arteriosclerotic peripheral vascular disease and coronary occlusion
3. Three cases of thromboangiitis obliterans and hypertension

RESULTS

1. *Arteriosclerotic peripheral vascular disease and hypertension.*—This group consisted of twenty patients, twelve men and eight women, ranging in age from 50 to 80 years. All had cardiac symptoms and presented abnormal findings on physical examination. The resting electrocardiograms in fourteen of these twenty patients were abnormal. The abnormalities were hypertrophy of the left ventricle with involvement of the ventricular muscle in ten cases, enlargement of the left ventricle in two cases, myocardial disease, one case, and right bundle branch block, one case.

Ballistocardiogram (Table IV): The resting ballistocardiographic tracings were abnormal in nineteen of these twenty subjects, and borderline in one. The abnormalities encountered most frequently were small to absent I waves (11 cases), and a combination of very small or absent I waves and deep K waves (3 cases).* In summary, among twenty patients with arteriosclerotic peripheral vascular disease and hypertension, none was found to have a completely normal ballistocardiogram at rest.

TABLE IV. COMPLICATED P.V.D. AND RESTING BALLISTOCARDIOGRAM

DIAGNOSIS	(PATIENTS OVER 50 YEARS)			
	TOTAL	NORMAL	ABNORMAL	BORDERLINE
Arteriosclerotic P.V.D.* and Hypertension	20	0	19	1
Arteriosclerotic P.V.D.* and Coronary Occlusion	3	0	3	0
Complicated T.A.O.†	3	0	3	0
Total	26	0	25	1

*Peripheral vascular disease
†Thromboangiitis obliterans

2. *Arteriosclerotic peripheral vascular disease and coronary occlusion.*—This group comprised three patients, all men, ranging in age from 70 to 74 years. The electrocardiograms showed previous anterior myocardial infarction in two cases and previous posterior myocardial infarction in one case.

Ballistocardiogram (Table IV): The resting ballistocardiographic tracings were all abnormal. There were small I waves (2 cases) and small I waves with deep K waves in the remaining case.

*Bizarre tracings occurred in two cases, and tiny I waves with notching of the J-K waves in three cases.

DISCUSSION

In order to determine the effect which peripheral vascular disease has upon the ballistocardiogram, sixty-five patients were studied. Of these, thirty-six had uncomplicated arteriosclerotic peripheral vascular disease or uncomplicated thromboangiitis obliterans. Among the thirty-six, who were under 50 years of age, twenty-eight had abnormal ballistocardiographic tracings. In three, the tracing was borderline. This is at variance with the findings in a normal control group,[9] in which the resting ballistocardiogram was abnormal in less than 7 per cent of the subjects below the age of fifty. Thus, it appears that peripheral vascular disease per se may produce an abnormal ballistocardiogram in the absence of cardiac disease.

In the second group of twenty-nine patients with peripheral vascular disease complicated by cardiac involvement, all the ballistocardiograms were abnormal—regardless of the age of the patients. In this group, one cannot ascertain the part played by the peripheral vascular disease in the production of the ballistic abnormalities.

Unfortunately, the patients with peripheral vascular disease, who had no apparent cardiac involvement, could not be studied with the Master "Two-step" test, because of their inability to perform exercise.

The ballistocardiograms were recorded by means of the Pordy dual ballistocardiograph* for standard recording of both photoelectric and electromagnetic tracings. The recording of standardized ballistocardiographic tracings using this apparatus is important, so that repeated records will be comparable.

The ballistocardiographic abnormalities found were nonspecific for arteriosclerotic peripheral vascular disease or thromboangiitis obliterans. This confirms the opinion of almost all the workers concerning the interpretation of abnormal ballistocardiographic records.

SUMMARY AND CONCLUSION

1. The ballistocardiographic findings in sixty-five cases with peripheral vascular disease are presented. This group included thirty-six cases with uncomplicated arteriosclerotic peripheral vascular disease and uncomplicated thromboangiitis obliterans. The ballistocardiograms were recorded by means of the Pordy dual displacement and velocity apparatus, a modified Dock-type instrument.

2. Of twenty-two patients under 50 years of age, with uncomplicated arteriosclerotic peripheral vascular disease, eighteen presented abnormal ballistocardiograms at rest. In two cases, the tracing was borderline.

3. Of fourteen patients under 50 years of age, with uncomplicated thromboangiitis obliterans, ten had abnormal resting ballistocardiograms. In one case, the tracing was borderline.

*Manufactured by the Mendelsohn Research Laboratories, Bloomfield, New Jersey.

4. In all cases of peripheral vascular disease, complicated by cardiac involvement, the resting ballistocardiograms were abnormal.

5. Abnormal ballistocardiographic patterns are not specific for any one particular peripheral vascular disease entity.

6. The majority of patients under fifty years of age with uncomplicated peripheral vascular disease have an abnormal ballistocardiogram.

We feel grateful to Doctor Lester Blum, in charge of the Peripheral Vascular Clinic, The Mount Sinai Hospital, New York, for placing the patients of the clinic at our disposal and for his complete cooperation. Iris Kanner lent us technical assistance for which we thank her.

REFERENCES

1. Dock, W., and Taubman, F.: Some Technics for Recording the Ballistocardiogram Directly From the Body, Am. J. Med. **7**:751, 1949.
2. Pordy, L., Chesky, K., Master, A. M., Taymor, R., and Moser, M.: The Dual Displacement and Velocity Ballistocardiograph Apparatus, AM. HEART J. **44**:248, 1952.
3. DeLalla, V., Jr., and Brown, H. R.: The Respiratory Variation of the Ballistocardiogram, Am. J. Med. **10**:728, 1951.
4. Starr, I.: On the Later Development of Heart Disease in Apparently Healthy Persons With Abnormal Ballistocardiograms. Eight to Ten Years After—Histories of 90 Persons Over 40 Years of Age, Am. J. M. Sc. **214**:233, 1947.
5. Dock, W., Mandelbaum, H., and Mandelbaum, R. A.: Ballistocardiograph in Medical Practice, J.A.M.A. **146**:1284, 1951.
6. Brown, H. R., Jr., Hoffman, M. J., and DeLalla, V., Jr.: Ballistocardiographic Findings in Patients With Symptoms of Angina Pectoris, Circulation **1**:132, 1950.
7. Makison, D. H.: Change in the Ballistocardiogram After Exercise in Normal and Abnormal Subjects, Circulation **2**:186, 1950.
8. Frankel, A. L., and Rothermick, N. O.: Clinical Experiences in Ballistocardiography, Ann. Int. Med. **36**:1385, 1952.
9. Pordy, L., Taymor, R. C., Moser, M., Chesky, K., and Master, A. M.: Clinical Evaluation of the Ballistocardiogram. I. Normal Subjects, AM. HEART J. **42**:321, 1951.
10. Chesky, K., Moser, M., Taymor, R. C., Master, A. M., and Pordy, L.: Clinical Evaluation of the Ballistocardiogram. II. Heart Disease—Hypertension, Angina Pectoris, and Myocardial Infarction, AM. HEART J. **42**:328, 1951.

THE EFFECTS OF OXYGEN BREATHING ON THE PULMONARY CIRCULATION IN MITRAL STENOSIS

M. McGregor, M.D. (Rand), M.R.C.P. (Lond.), T. H. Bothwell, M.B., B.Ch. (Rand), M.R.C.P. (Lond.), M. M. Zion, M.B., B.Ch. (Rand), and B. A. Bradlow, M.D. (Rand)

Johannesburg, South Africa

UNTIL recently studies on the circulatory dynamics of the pulmonary circuit have been confined to experimental animals and to normal human subjects. In 1947, a review of the results of such studies led Cournand[1] to the conclusion that "demonstration of vaso-motor effects in the pulmonary circulation of man is still wanting." Since then, however, investigation of cases of mitral stenosis has demonstrated that a sharp rise in pulmonary vascular resistance takes place in this condition as the pulmonary capillary pressure rises,[2] and that this rise is at least partially reversible following mitral valvotomy.[3] The mechanism of this rise has not yet been elucidated. While Lewis and his co-workers[2] regarded the phenomenon teleologically as a means of protecting the pulmonary capillary bed from unduly high pressures Westcott and his colleagues[4] have suggested that it is the result of anoxia secondary to pulmonary congestion and edema. The latter suggestion is supported by the demonstration that anoxia causes a rise in pulmonary artery pressure both in anaesthetized cats[5,6] and in unanaesthetized normal human subjects.[4,7,8]

The following investigation was performed in order to study the effects of the breathing of high concentrations of oxygen on the pulmonary hypertension found in mitral stenosis.

MATERIAL

Thirteen subjects with mitral valve disease were selected for study. Clinical, radiographic, electrocardiographic, phonocardiographic, and surgical data are summarized in Table I from which it will be seen that mitral stenosis was considered to be the principal lesion in Patients 1-12, while mitral regurgitation was considered predominant in Patient 13.

METHODS

On the day preceding the study the patient was made familiar with the techniques of collecting expired air. After a light breakfast the patient was placed in a recumbent or semirecumbent position on the roentgenographic table and a

From the Department of Medicine, University of the Witwatersrand and Johannesburg Hospital, and Cardio-Pulmonary Research Unit of the Council for Scientific and Industrial Research.

This work was carried out with the technical assistance of Joanna Whidborne, B.Sc. (Hons) (Lond.), J. P. Shreve, and H. I. Goldman, B.Sc. (Hons) (Rand).

Received for publication March 5, 1953.

TABLE I

PATIENT NUMBER	DIAGNOSIS		CLINICAL DATA								ECG DATA				RADIOLOGICAL DATA					SURGICAL DATA	
	MITRAL STENOSIS	MITRAL INCOMPETENCE	AGE	SEX	FUNCTION (BAKER AND ASSOCIATES[21])	ORTHOPNEA	HEMOPTYSES	VENOUS CONGESTION	DURATION OF CCF (MONTHS)	LT. VENTRICULAR ENLARGEMENT	AORTIC INCOMPETENCE	APICAL SYST. MURMUR (LEVINE[20])	AURICULAR FIBRILLATION	NOTCHED "P" WAVES	RT. VENT. HYPERTROPHY (SOKOLOW[23])	LT. VENT. HYPERTROPHY (SOKOLOW[23])	CARDIO-THORACIC RATIO (%)	LT. VENT. ENLARGEMENT	RT. VENT. ENLARGEMENT	LT. AUR. ENLARGEMENT	SYSTOLIC EXPANSION LEFT AURICLE	REGURGITANT STREAM	VALVE CIRCUMFERENCE (INCHES)
1	+	+	35	M	4	+	+	+	6+			3		+		+	48			+	+	0.8
2	+	+	19	F	4	+		+	4			3				+	61	+	+	+		0.3
3	+		37	F	3	+			0								41			+		0.8
4	+		28	F	2		2		0								44			+		
5	+	+	40	M	2				0	+		4		+			42			+		1.1
6	+		40	M	3	+	3		0								40		+	+		1.1
7	+	+	40	F	4	+		+	36			3	+		+	+	55			+		1.1
8	+		37	F	3	+	1		0						+	+	54	+	+	+	+	
9	+		23	F	1				0								48			+		0.6
10	+	+	27	F	1*	+	1		0		+	3	+		+	+	50			+	+	0.8
11	+	+	32	F	4	+	1	+	12**			4					54	+	+	+		1.2
12	+		25	F	3		+		0			1	+	+	+		46	+	+	+		
13	+	+	21	F	3	+			0		+	3				+	60	+	+	+	+	0.8

*Grade 3 during previous pregnancy. Developed acute pulmonary edema when 3 months pregnant, 5 months after this assessment.
**In failure 6 years previously when pregnant.
CCF = Congestive cardiac failure
ECG = Electrocardiogram

cardiac catheter was passed under radiographic control as far as possible into the pulmonary artery. Light sedation (Nembutal) was occasionally employed in excitable subjects. "Pulmonary capillary pressures"[9] were then recorded* and the catheter tip withdrawn to the main pulmonary trunk. Pressures were then recorded at approximately 5 minute intervals until a base line had become established. At this time mixed venous and femoral arterial samples were withdrawn. In seven patients (Nos. 6 to 13) a three-minute sample of expired air was collected at the same time for estimation of oxygen consumption. When this procedure produced a rise in pulmonary artery pressure, arterial and mixed venous samples were again withdrawn after the pressure had returned to the base line. One hundred per cent oxygen was then breathed and pulmonary arterial pressures were recorded at approximately minute intervals until a new base line was established. Blood samples were withdrawn again and in Patients 3, 6, 7, 12, 13 the oxygen uptake was determined by breathing from an oxygen filled spirometer. The face piece then was removed but observations were continued in Patients 9 to 12 for a further period ranging from 9 to 18 minutes (see Table II).

An identical rate of oxygen consumption, whether air or pure oxygen is breathed, has been demonstrated by Donald and Christie,[10] and in our studies in which this estimation was made both before and during oxygen administration there was close agreement. When both estimations were made the uptake during air breathing was used for calculating the cardiac output. In three patients (Nos. 1, 4, 5), because of technical difficulties, oxygen consumption was not measured. In these the cardiac output calculations are based on the arbitrary figure for oxygen uptake of 200 ml./minute and cannot be looked on as absolute although the trends demonstrated are valid.

From the results recorded cardiac output and total pulmonary resistance[2] were calculated.

RESULTS

The results of all experiments are shown in Table II and as an illustration the results from Patient 11 have been represented graphically (Fig. 1).

In nine patients there was some initial anoxia present as shown by an arterial oxygen saturation below 91 per cent, the lower limit† of normal.[11,12] The initial "pulmonary capillary" mean pressure was raised in all patients (10 to 37 mm. Hg). The mean pulmonary artery pressure immediately before oxygen administration was also raised in every patient (16/78 mm. Hg) and fell after oxygen administration in each instance. The total pulmonary resistance also fell significantly in ten of the thirteen experiments. When oxygen was stopped the pulmonary artery pressure again rose in all patients although the preoxygen level was not reached during the period of observation (see Fig. 1).

---

*Sanborn electromanometer. Reference point 5 cm. posterior to the sternal angle.

†Altitude 5,750 feet above sea level.

TABLE II. CATHETERIZATION DATA IN THIRTEEN CASES OF MITRAL DISEASE

CASE	INITIAL P.Cm.	INITIAL ART. O_2 (%)	PERIOD	TIME (MINS.)	C.O.	P.Am.	T.PU.R.	P.Am. CHANGE (%)	T.PU.R. CHANGE (%)
1	37	84.8	A	− 1	2.95	78	2120		
			B	5	2.64	70	2120	−10	0
2	30	79.4	A	− 1	1.96	78	3180		
			B	6	1.92	65	2705	−16	−15
3	25	91.0	A	− 3	3.52	42	955		
			B	6	3.31	30	726	−29	−24
4	20	99	A	− 1	3.88	30	620		
			B	6	3.62	20	444	−33	−28
5	12	88.6	A	− 2	3.78	18	380		
			B	5	3.38	16	378	−10	0
6		85.6	A	− 3	2.80	26	744		
			B	7	3.73	20	429	−23	−42
7		93.3	A	− 2	2.57	20	623		
			B	12	2.78	18	518	−10	−17
8	25	89	A	− 4	2.28	50	1752		
			B	14	2.00	35	1400	−30	−21
9		90.4	A	− 1	4.74	68	1148		
			B	5	5.30	40	604	−41	−47
			C	16	5.65	60	850		
10	10		A	− 1	5.40	17	253		
			B	5	4.97	11	176	−35	−30
			C	6	5.38	17	257		
11		94.2	A	− 1	2.48	62	2040		
			B	9	2.99	40	1071	−36	−48
			C	16	2.51	50	1600		
12	30	88.3	A	− 5	3.57	27	605		
			B	5	3.39	25	590	− 7	− 3
			C	18	3.86	30	621		
13	10	89.9	A	−10	1.92	20	835		
			B	10	2.00	11	440	−45	−42

Period A = Observations recorded immediately before initiation of oxygen breathing (exact time being indicated in next column).

Period B = Observations recorded after a varying period of oxygen breathing. (Number of minutes after initiation of oxygen breathing indicated in next column.)

Period C = Observations recorded after discontinuation of oxygen breathing. (Time since discontinuation of oxygen indicated in next column.)

P.Am. = Mean pulmonary artery pressure (mm. Mercury).

P.Cm. = Mean pulmonary capillary pressure (mm. Mercury).

C.O. = Cardiac output (Liters per minute).

T.Pu.R. = Total Pulmonary resistance (dynes sec. cms. $^{-5}$).

It can be seen in Fig. 2 that there is some correlation between the initial mean pulmonary artery pressure and the fall in total pulmonary resistance, although the series is too small to provide conclusive statistical evidence of this ($r = 0.46$, S.E. $= 0.29$). There appears, however, to be a complete lack of correlation between the initial arterial oxygen saturation and the fall in total pulmonary resistance, ($r = 0.093$, S.E. $= 0.29$), (Fig. 3).

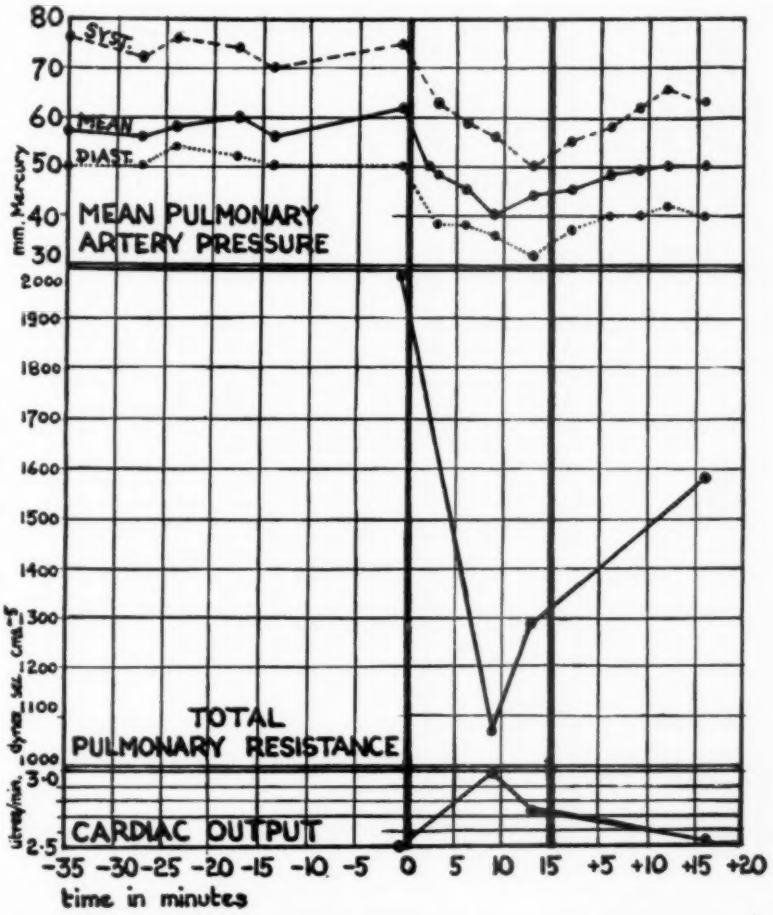

Fig. 1.—Illustrating the changes in mean pulmonary artery pressure, cardiac output, and total pulmonary resistance in Patient 11.

DISCUSSION

It has been demonstrated previously that breathing pure oxygen for short periods produces a fall in the pulmonary artery pressure in cases of mitral stenosis.[13] Studies designed to show whether this is the result of a fall in cardiac output or a reduction in pulmonary vascular resistance have not yet been reported. A reduction in the arterial oxygen saturation in mitral stenosis has also been demonstrated though it is uncertain whether this is the result of diffusion impairment or venous admixture.[14]

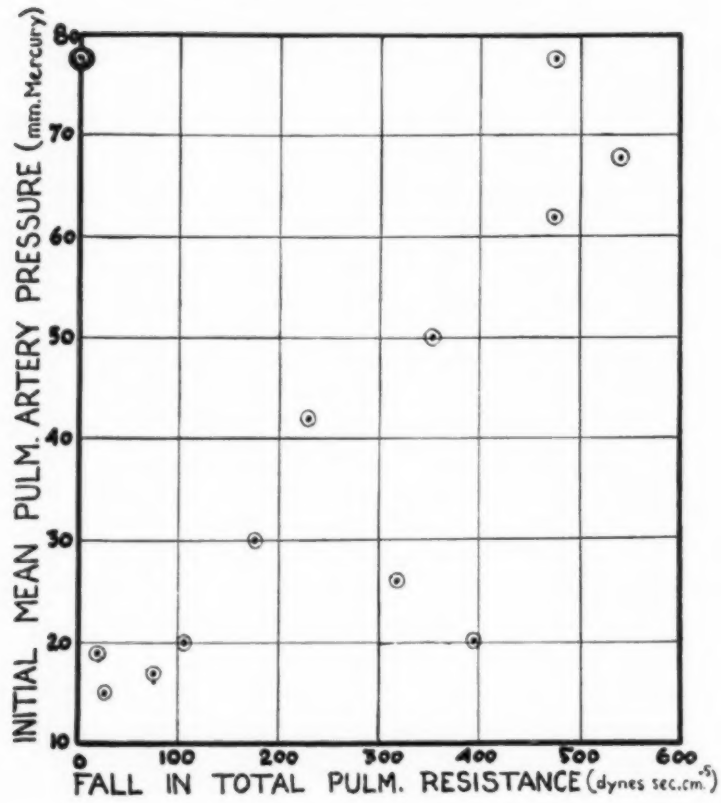

Fig. 2.—The correlation between the initial mean pulmonary artery pressure and the fall in total pulmonary resistance with oxygen administration.

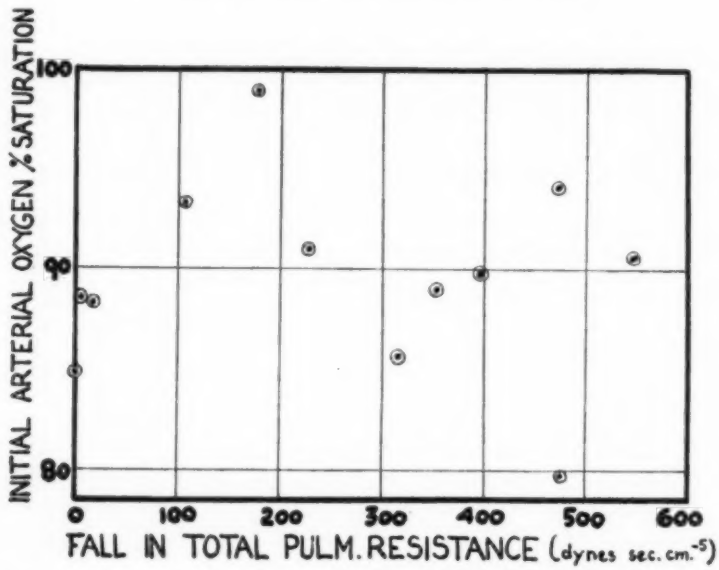

Fig. 3.—The correlation between the initial arterial oxygen saturation and the fall in total pulmonary resistance with oxygen administration.

These facts coupled with the fall in total pulmonary resistance observed in ten of our thirteen patients while breathing oxygen lend some support to the supposition of Westcott and his co-workers,[4] that the high vascular resistance in cases of mitral stenosis is initiated by a degree of anoxia following on capillary congestion and early edema formation. The absence of correlation between the initial arterial oxygen saturation and the fall in resistance observed does not necessarily invalidate such a conclusion. Westcott and associates[4] have demonstrated a complete absence of correlation between the fall in oxygen saturation and the rise in pulmonary resistance in a group of normal subjects where the pulmonary resistance had been artificially elevated by means of breathing 13 per cent oxygen in nitrogen. In addition in some chronic cases of mitral stenosis marked pathologic changes take place in the pulmonary vasculature[15,16] which must give rise to a varying increase in resistance not immediately reversible. This presumably accounts for the pulmonary hypertension which has been shown to persist for months following successful valvotomy[17] (Unpublished data). Only in the mildest cases reported here did the pulmonary artery pressure fall to normal limits as a result of oxygen administration, and it is possible that the amount, by which the peripheral resistance remains above normal after anoxia has been abolished by oxygen breathing, will be an index of the extent to which irreversible pathologic arterial changes have taken place.

Although it seems possible that anoxia may be a factor initiating increased pulmonary resistance in these cases, it is not the only one, as injection of the autonomic blocking agent Tetraethylammonium Chloride has been shown to lower pulmonary vascular resistance in man when this is pathologically raised.[18] In addition, Condorelli,[19] has demonstrated that pulmonary vascular resistance may be elevated by administration of pharmacological doses of noradrenaline. It would seem, therefore, that the autonomic nervous system may play some part in the elevation of pulmonary resistance in some cases.

SUMMARY AND CONCLUSIONS

1. Administration of pure oxygen to thirteen subjects with raised pulmonary artery pressure and raised pulmonary resistance produced a fall in pulmonary pressure in all instances. In ten there was an additional significant fall in total pulmonary resistance.

2. There was some correlation between the initial pulmonary pressure and the degree of fall in vascular resistance.

3. There was no correlation between initial arterial anoxia and the fall in pulmonary resistance following oxygen. In spite of this it is felt that local anoxia caused by pulmonary congestion and edema may at least play some part in the development of pulmonary hypertension in mitral stenosis.

The authors wish to express their gratitude to Dr. J. H. Gear for advice in the preparation of this paper, to Dr. J. Kaye and Dr. J. Meyer and Mr. J. J. O'Connor of the Department of Radiology for the great assistance they have given during these investigations, to Mr. A. M. Shevitz and Miss M. Hills for the photographic reproductions and typing, respectively, and finally to Professor G. A. Elliott, in whose department this work was carried out, for encouragement and help in the preparation of this paper.

REFERENCES

1. Cournand, A.: Recent Observations on the Dynamics of the Pulmonary Circulation, Bull New York Acad. Med. **23**:27, 1947.
2. Lewis, B. M., Gorlin, R., Houssay, H. E. J., Haynes, F. W., and Dexter, L.: Clinical and Physiological Correlations in Patients With Mitral Stenosis. V., Am. Heart J. **43**:2, 1952.
3. Draper, A., Heinbecker, R., Daley, R., Carrell, D., Mudd, G., Wells, R., Folholt, E. W., Andrus, E. C., and Bing, R. J.: Physiologic Studies in Mitral Valvular Disease, Circulation **3**:531, 1951.
4. Westcott, R. M., Fowler, N. O., Scott, R. C., Hauerstein, V. D., and McGuire, J.: Anoxia and Human Pulmonary Vascular Resistance, J. Clin. Investigation **30**:957, 1951.
5. Von Euler, U. S., and Liljestrand, G.: 1947. Reported by Motley and associates.[7]
6. Liljestrand, G.: Regulation of Pulmonary Arterial Blood Pressure, Arch. Int. Med. **81**:162, 1948.
7. Motley, H. L., Cournand, A., Werkö, L., Himmelstein, A., and Drysdale, D.: Influence of Short Periods of Induced Acute Anoxia Upon Pulmonary Artery Pressures in Man, Am. J. Physiol. **150**:315, 1947.
8. Doyle, J. T., Wilson, J. S., and Warren, J. V.: Pulmonary Vascular Responses to Short Term Hypoxia in Human Subjects, Circulation **5**:263, 1952.
9. Hellems, H. K., Haynes, F. W., Gowdy, J. F., and Dexter, L.: Pulmonary "Capillary" Pressure in Man, J. Clin. Investigation **27**:540, 1948.
10. Donald, K. W., and Christie, R. V.: A New Method of Clinical Spirometry, Clin. Sc. **8**:21, 1949.
11. Becklake, M. R.: Personal communication, 1947.
12. Stammers, A. D.: Oxygen Content, Capacity and Percentage Saturation in Arterial Blood at Johannesburg (Altitude 5,750 ft.), J. Physiol. **78**:21, 1933.
13. Dressler, S. H., Slonim, N. B., Balchum, O. J., Bronfin, G. J., and Ravin, A.: The Effect of Breathing 100% Oxygen on the Pulmonary Arterial Pressure in Patients With Pulmonary Tuberculosis and Mitral Stenosis, J. Clin. Investigation **31**:807, 1952.
14. Blount, S. G., Jr., McCord, M. C., and Anderson, L. L.: The Alveolar-Arterial Oxygen Pressure Gradient in Mitral Stenosis, J. Clin. Investigation **31**:840, 1952.
15. Parker, F., Jr., and Weiss, S.: The Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis, Am. J. Path. **12**:573, 1936.
16. Henry, E. W.: The Small Pulmonary Vessels in Mitral Stenosis, Brit. Heart J. **14**:406, 1952.
17. Soulie, P., Joly, F., Carlotti, J., Voci, G., and Serville, M.: The Treatment of Mitral Stenosis by Commissurotomy: Indication and Post-Operative Results. Abstracts of Scientific Communications to the European Congress of Cardiology, Kent, England, 1952, Thanet Press.
18. Fowler, N. O., Westcott, R. N., Hauerstein, V. D., Scott, R. C., and McGuire, J.: Observations on Autonomic Participation in Pulmonary Arteriolar Resistance in Man, J Clin. Investigation **29**:1387, 1950.
19. Condorelli, L.: J.A.M.A. **149**:1485, 1952.
20. Levine, S. A., and Harvey, W. P.: Clinical Auscultation of the Heart, London, 1949, W. B. Saunders and Company.
21. Baker, C., Brock, R. C., Campbell, M., and Wood, P.: Valvotomy for Mitral Stenosis, Brit. M. J. **1**:1043, 1952.
22. Sokolow, M., and Lyon, T. P.: The Ventricular Complex in Left Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads, Am. Heart J. **37**:160, 1949.
23. Sokolow, M., and Lyon, T. P.: The Ventricular Complex in Right Ventricular Hypertrophy as Obtained by Unipolar Precordial Leads, Am. Heart J. **38**:273, 1949.

A REFERENCE POTENTIAL FOR UNIPOLAR ELECTROCARDIOGRAPHIC MEASUREMENTS ON MODELS

ERNEST FRANK, PH.D., AND CALVIN F. KAY, M.D.

PHILADELPHIA, PA.

ELECTROCARDIOGRAPHIC theory and practice have progressively utilized field analysis techniques. At the least, a useful mathematical basis for the integration of electrocardiographic data upon a semiempirical basis has been provided. Ideally, the theoretical concepts applied could provide a key to the reduction of the element of empiricism in electrocardiographic interpretation. For this latter purpose, it is necessary to make certain assumptions regarding the electrical representation of the heart, the shape of the human torso, and the conducting properties of the body tissues. Quantitative estimates of the magnitude of the errors involved in these assumptions have not been established; hence, the accuracy of the conclusions drawn from the application of field analysis to electrocardiography, other than on a semiempirical basis, remains uncertain. In this laboratory, quantitative investigations of the accuracy of the application of dipole heart-field theory to electrocardiographic interpretation are being conducted using torso-shaped models.

It is essential in these studies to establish a fixed reference potential that is independent of the field distribution within and on the torso. With such a reference potential it becomes possible to obtain quantitative results which are pertinent to the evaluation of the accuracy and validity of many of the currently applied theories of electrocardiography. For example, model studies employing a suitable reference potential system may be used to estimate the departure of the Wilson central terminal from the true zero reference, to study the errors inherent in heart-vector projection, and to evaluate the various spatial reference systems used in current three-dimensional vectorcardiography.

A part of the investigations involves the use of torso-shaped models filled with a homogeneous conducting fluid. When a finite dipole* is immersed in a model of this kind, the potential distribution over the torso boundary is similar to that produced on the human subject by electrical activity of the heart at a given instant of time.

From the Electromedical Group, Research Division, Moore School of Electrical Engineering, University of Pennsylvania, and the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

This investigation was supported in part by grants of the National Heart Institute, United States Public Health Service.

Received for publication Feb. 6, 1953.

*A finite dipole is defined as a current source and sink separated by a finite distance *d*. A finite dipole differs from a mathematical dipole, since the latter source-sink pair has infinitesimal separation with a finite product of source-sink strength times separation.

Equipotential maps (or contours) on the insulating torso boundary can be determined under a given set of conditions by making potential difference measurements from a fixed boundary point to various other points on the boundary. Such "bipolar" measurements can be performed for various torso shapes, various dipole positions and orientations, various conducting media, and under other conditions. However, with the sole use of bipolar measurements it is not possible to obtain a direct comparison between equipotentials measured under two different sets of conditions, although the general behavior of the equipotential contours may be studied.

An illustration of this limitation of bipolar measurements is shown in Fig. 1 where a hypothetical example of equipotentials is given for the same torso with two different positions of the immersed dipole. In both of the cases shown the

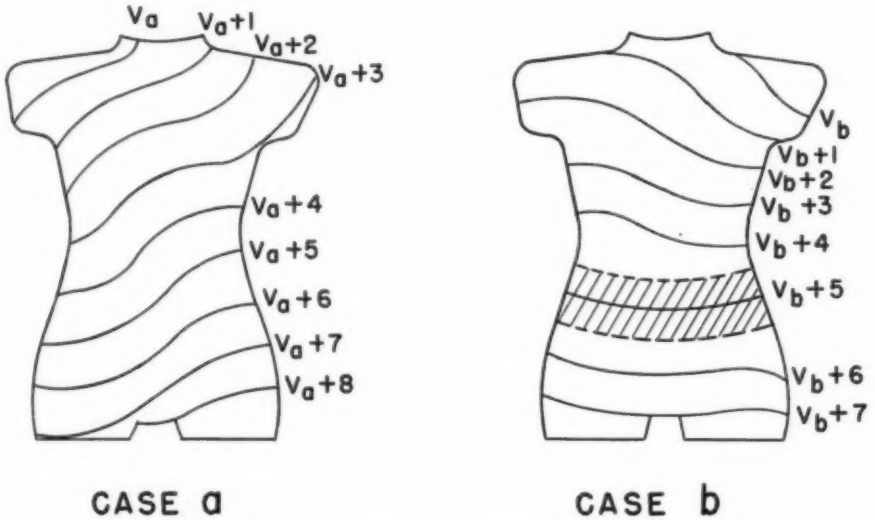

Fig. 1.—Illustrative equipotentials spaced 1 mv. apart on an insulating torso filled with homogeneous conducting fluid for two different positions of an immersed dipole. (See text for details.)

equipotentials are spaced 1 mv. apart, but the potential of a given line in case *a* is not known relative to any of the lines of case *b*. For example, it might be that equipotential $V_a + 4$ is at the same potential relative to the dipole as is equipotential $V_b + 3$, but this cannot be known without a relationship between V_a and V_b which is not provided by the bipolar data. Yet, the ability to identify the shift of specific equipotentials owing to various changes of the physical system is important in investigating the accuracy of many applications of electrocardiographic theory.

THE REFERENCE POTENTIAL

A reference potential V_r fixed with respect to the current source and independent of the characteristics of the current field would provide the necessary key to the direct comparison of equipotentials. Both $V_a - V_r$ and $V_b - V_r$ could be measured and then $V_a - V_b$ could be computed.

It is desirable to establish V_r as the potential at the electrical mid-point between the two current electrodes, the reference potential commonly used in electrocardiographic theory. The value assigned to this V_r is conventionally zero. One might expect that such a V_r could be found at the junction point of equal resistors connected between V_1 and V_2 of Fig. 2, exactly dividing the applied voltage V. Experimentally, this V_r derived from V/2 is completely unsatisfactory because of electrode polarization[1] which manifests itself as a discontinuity in potential between electrode and liquid.

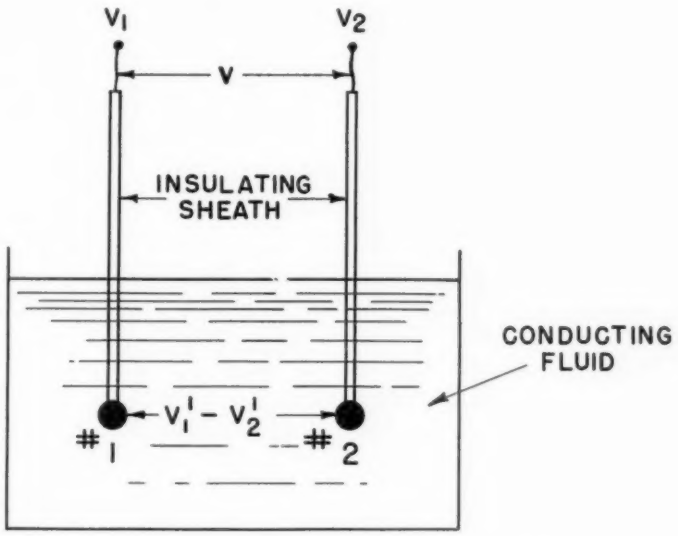

Fig. 2.—Two electrodes immersed in a conducting fluid.

A precise definition of the electrical mid-point V_r between two electrodes immersed in a conducting fluid may be made in terms of the following quantities:

V_1 = the potential of electrode 1.
V_2 = the potential of electrode 2.

V_1' = the potential on the liquid side of electrode 1.

V_2' = the potential on the liquid side of electrode 2.

$\Delta V_{p1} = V_1 - V_1'$ = the potential difference across electrode 1 interface resulting from polarization.
$\Delta V_{p2} = V_2 - V_2'$ = the potential difference across electrode 2 interface resulting from polarization.

The potential difference $V_1' - V_2'$ which is, so to speak, the potential difference "seen" by the liquid is effective in producing current in the medium. Consequently, the electrical mid-point between the two electrodes which is the reference potential desired is

$$V_r = \tfrac{1}{2}(V_1' + V_2'). \qquad (1)$$

In terms of the potentials applied to the electrodes

$$V_r = \tfrac{1}{2}(V_1 + V_2) - \tfrac{1}{2}(\Delta V_{p1} + \Delta V_{p2}). \quad (2)$$

It can be seen from Equation (2) that if $\Delta V_{p1} = -\Delta V_{p2}$, an unattainable ideal, then V_r could be derived from $V_1 + V_2$. However, the potential discontinuities at the electrode interfaces differ so much that neglecting ΔV_{p1} and ΔV_{p2} in Equation (2) results in errors in V_r which are approximately two orders of magnitude greater than the tolerable amount in typical cases.

The reference potential defined by these equations coincides with that which is defined theoretically by the Wilson central terminal.[2] It is the usual zero reference used in electrocardiography. The definition and use of the reference potential of Equation (1), therefore, enable a direct comparison of experimental results with theoretical predictions, as well as permitting different sets of relative data of the kind cited in Fig. 1 to be tied together closely.

A suitable procedure for determining the reference potential V_r experimentally is to accurately align the finite dipole along the axis of a symmetrical insulating container, such as midway between the ends of a vertical insulating cylinder filled with a homogeneous conducting fluid. The alignment may be accomplished by optical sighting which is made possible by the use of a transparent cylinder wall. From symmetry it is known that V_r is the equipotential which lies in the plane perpendicular to the dipole axis and passing through the geometric center between the two electrodes. The accuracy of the dipole alignment and the accuracy of the equipotential circle V_r, scored on the cylinder wall, are important factors in determining the over-all error in the reference potential. Reproducibility tests can be used to evaluate a portion of this error.

With V_r established in this way, the potential of a junction point between two resistors connected across the electrode lead-in wires can be adjusted to be equal to V_r, using a null detector connected between this junction point and the known location of V_r on the cylinder boundary. (In practice, a very delicately balanced bridge, including capacitance balance, is required and is discussed later.) When the dipole is later immersed in an unsymmetrical system, the boundary voltages of that system can be measured with respect to the resistor junction which remains at the potential V_r. Such measurements are called "unipolar."

ACCURACY REQUIREMENTS

The accuracy with which the reference potential can be determined experimentally and its constancy over a period of time impose a limit on its practical use. For example, suppose that in correlating the data of Fig. 1, $V_a - V_b$ is calculated to be -1 mv. $\pm$ ½ mv., where $\pm$ ½ mv. is the error due to the uncertainty of V_r which includes both instrument and fluctuation errors. Then $V_a = V_b - 1$, nominally, and equipotential $V_a + 6$ corresponds to equipotential $V_b + 5$. However, the uncertainty of the correlation is $\pm$ ½ mv., so the equipotential corresponding to $V_a + 6$ could lie anywhere in the shaded region of Fig. 1, the range $V_b = 4.5$ to $V_b = 5.5$. As another illustration, it can readily be seen that measurements of the departures of the Wilson central terminal potential from the true zero reference, V_r, are directly dependent upon the accuracy with which V_r itself is known.

The required accuracy of V_r can be discussed with reference to Fig. 3 where a finite dipole is shown immersed in an inverted torso model. The potential difference V is applied to the finite dipole and the current I distributes itself throughout the conducting medium as suggested by the dashed lines. The solid lines on the torso boundary represent equipotentials where V_r is identified as well as V_m, the maximum potential observed on the boundary relative to V_r.

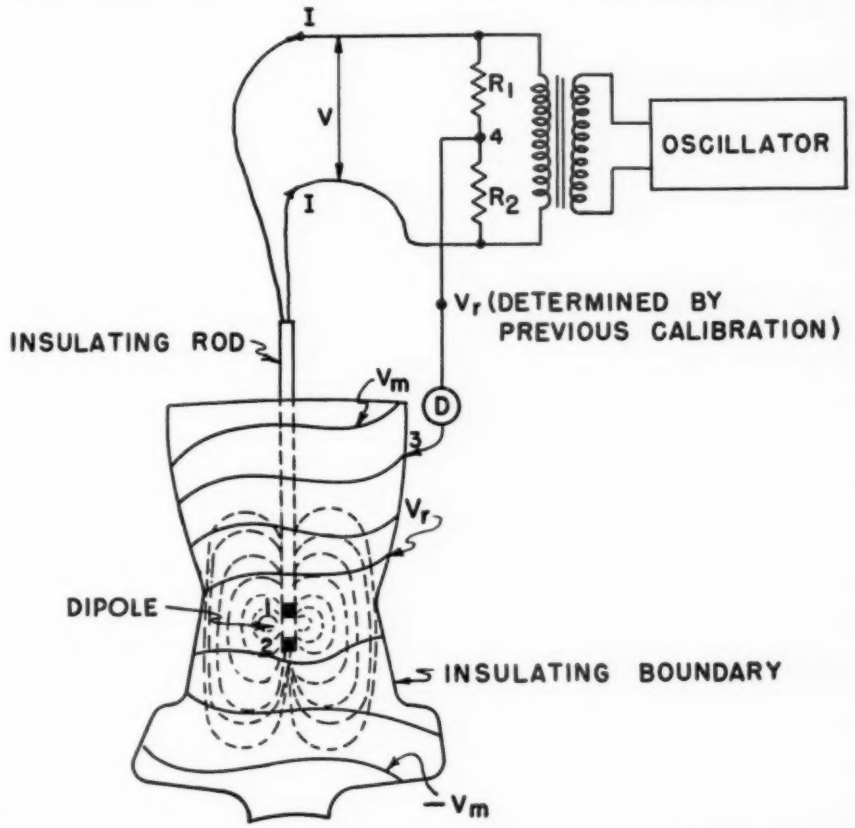

Fig. 3.—Current lines and equipotentials produced by a dipole immersed in a torso filled with conducting fluid. The torso is inverted for convenience in observing and adjusting the finite dipole position and orientation. Contact with the conducting medium, such as point 3, is made at the boundary by watertight electrodes (not shown) affixed to the insulated torso.

By the use of platinum current electrodes coated with platinum black[3] the finite dipole resistance is given, approximately, by $R = k_1 \rho$ where k_1 is a constant and ρ is the resistivity of the medium. Also, the dipole current is approximately $I = V/R$. In general, the boundary potential $V_B = V_B - V_r$ with $V_r = 0$ can be expressed as $V_B = I\ \rho\ f(r, \Theta, \phi)$ where $f(r, \Theta, \phi)$ is some function of the position point r, Θ, ϕ on the boundary (r, Θ and ϕ are standard polar spherical coordinates). Hence, $V_m = k_2 I \rho$ where k_2 is a constant representing f at the points where V_m occurs. Combining the relations for V_m, I, and R

$$V_m = k_2 I \rho = k_2 \frac{V\rho}{R} = k_2 \frac{V\rho}{k_1 \rho} = KV \quad , \quad K = \frac{k_2}{k_1} \quad . \tag{3}$$

This interesting result shows that V_m is some constant K times the applied voltage V, independent of the resistivity of the medium to a good first approximation, if the polarization effects are small. For a typical finite dipole which is limited in spacing d in order to achieve essentially mathematical dipole behavior as seen from the torso boundary and which is limited in electrode area so as to be insertible into cadavers, a representative empirical value of K is approximately 0.005.[4] Thus, $V_m = 0.005V$.

Suppose it is desired to determine equipotentials on the torso at intervals of $0.1V_m$; this will give a total of approximately twenty equipotential lines which define the contour behavior quite well. Further, a permissible inaccuracy of ±10 per cent under worse conditions may be stipulated. This establishes the permissible tolerance on V_r; namely, $\pm 0.01V_m$, for with an uncertainty of this amount the equipotential $0.1V_m$ will be determined to $0.1V_m \pm 0.01V_m$. This is the least favorable equipotential; V_m itself will be known to within ±1 per cent.

Since $V_m = 0.005V$, the accuracy with which V_r must be determined relative to V is established; namely, to within ±0.005 per cent of V. In terms of setting V_r at the junction of the resistors R_1 and R_2 shown in Fig. 3, this means that the setting must be determined to one part in 20,000! An inquiry into the physical reason for the need of such a precise determination of V_r discloses that the current density in the medium diminishes very markedly with distance from the dipole. Therefore, most of the potential drop takes place in the immediate vicinity of the dipole. If equal-increment equipotentials which span the potential-difference range V are considered, it can be seen that only 1 per cent of these will occur on the boundary, the remaining 99 per cent exist inside the torso, becoming more densely packed near the dipole. Therefore, if V_r is to be determined to within ±1 per cent of the maximum boundary potential the reasons for such stringent requirements become evident.

In typical field mapping arrangements often encountered in electrical engineering, the equipotentials of interest encompass the entire applied voltage range V rather than only 1 per cent of V as in this case. Hence, the same accuracy in the determination of equipotentials can be achieved in many cases with only 1/100 of the precision in the setting of the resistor junction. Furthermore, in such typical field mapping problems, large area electrodes and special conducting solutions (such as copper and copper sulphate)[5] can usually be employed to render negligible the influence of electrode polarization. But in the finite dipole system the electrode area is severely limited, as stated previously, and, moreover, it is desirable to devise a system capable of being used with physiologic conducting media. As a consequence, electrode polarization effects cannot be entirely circumvented and result in an impairment of accuracy (manifested as an instability in V_r owing to fluctuations in polarization effects) amounting to an estimated factor of at least 10, mainly on the basis of electrode area. Thus, the over-all accuracy required in the torso system is in the vicinity of 1,000 times that needed in conventional field mapping and poses an unusually severe measurement problem.

EQUIVALENT BRIDGES

An exceedingly helpful viewpoint giving additional insight into the kind of measurement techniques that can be employed is provided in terms of equivalent bridge circuits. The electrical effects in the system of Fig. 3 can be understood in terms of an equivalent bridge circuit, evolved by replacing the conducting fluid by equivalent electrical elements as shown in Fig. 4. In this figure the conducting medium is replaced by equivalent lumped circuit elements as follows:

C_{p1} and R_{p1} represent the polarization impedance at the interface of electrode 1.

C_{p2} and R_{p2} represent the polarization impedance at the interface of electrode 2.

R_s represents the solution resistance through which substantially all of the current flows.

R_a represents the equivalent resistance between the probe (3) and the liquid side of electrode 1.

R_b represents the equivalent resistance between the probe (3) and the liquid side of electrode 2.

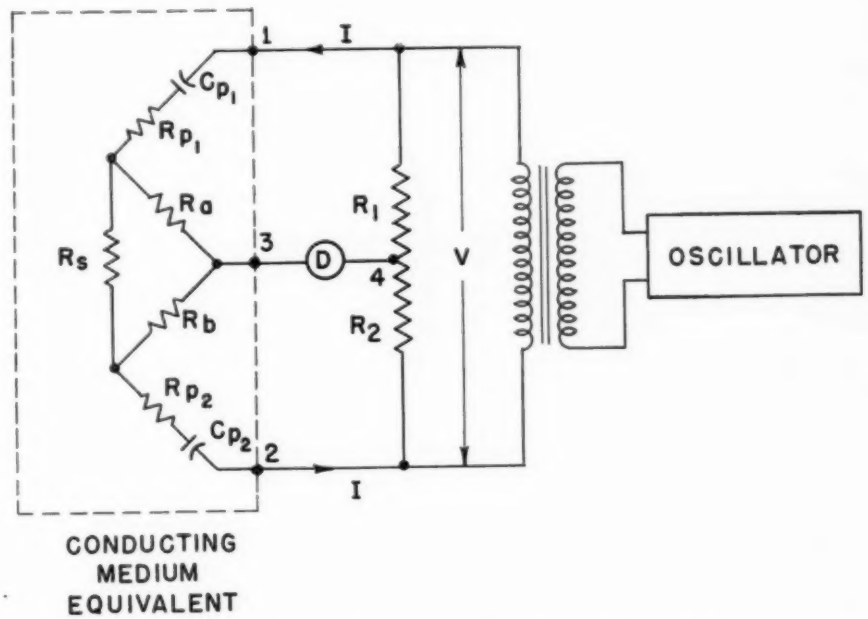

Fig. 4.—Equivalent bridge circuit for the finite dipole system of Fig. 3.

The detector has a high impedance in comparison with the bridge arms; as a consequence, the detector draws negligible current and the polarization impedance of the probe is negligible. Resistors R_a and R_b are much larger than the equivalent solution resistance R_s since the probe is small and intercepts very few current lines.

A simplification of the bridge circuit results when the delta-connected resistors R_s, R_a and R_b are replaced by an equivalent wye,[6] as indicated in Fig. 5, using the excellent approximations $R_a >> R_s$ and $R_b >> R_s$. The resistance $\frac{R_a R_b}{R_a + R_b}$ appears in series with D, which has a high impedance already and can be also bled into D. The simplified bridge circuit is shown in Fig. 6.

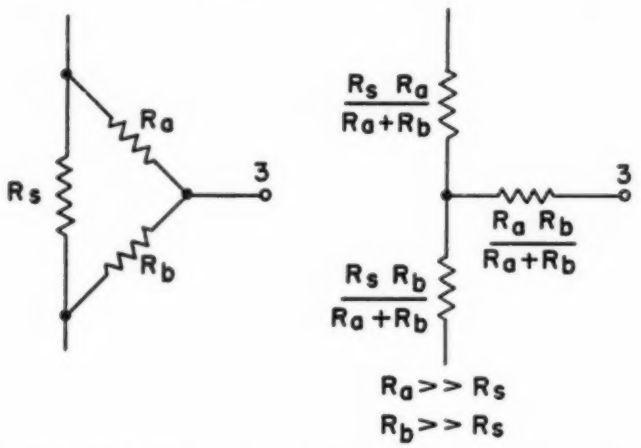

Fig. 5.– Delta-wye transformation of the three resistors representing the medium in order to simplify the bridge circuit of Fig. 4.

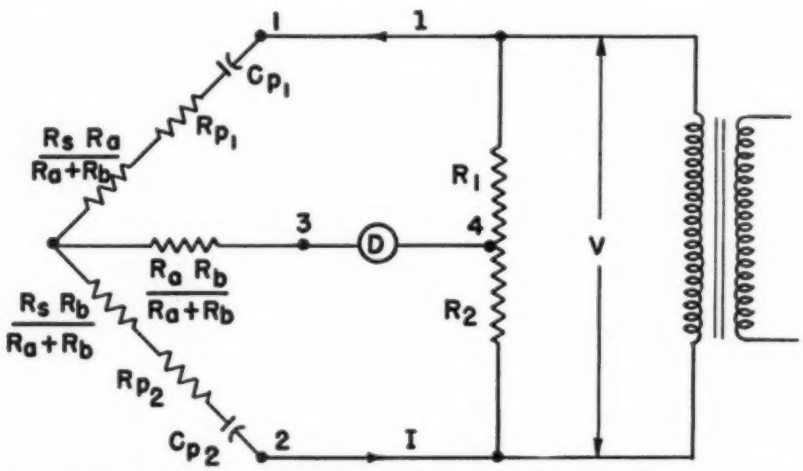

Fig. 6.—The bridge circuit of Fig. 4 with the resistance delta replaced by its equivalent wye. R_a and R_b are assumed to be much larger than R_s.

Since the required bridge null is 1/20,000 times V and the polarization impedances are unequal and not negligible, it is essential to incorporate capacitors (not shown) across the resistors R_1 and R_2 in order to balance the capacitive polarization effects as well as to compensate for stray circuit capacitance which is unavoidable and appreciable when striving for a 20,000:1 bridge null (see Fig. 10). The bridge balance is extremely delicate and suffers from the presence of the polarization impedances which are in the bridge arms. The inconstancy of these impedances, which carry the full dipole current, is a source of considerable difficulty in making such a reference potential system practical.

Bipolar measurements have been regarded ordinarily as simply potential difference measurements. However, replacing the conducting medium by equivalent electrical elements discloses that bipolar measurements are essentially bridge measurements in the same sense as the system just considered. Figure 7 illustrates an inverted torso with an immersed finite dipole and a voltmeter D connected for bipolar measurements. The equivalent bridge circuit which accompanies the actual system discloses the bridge nature of these measurements. Moreover, it can be seen that the polarization impedances of the dipole do not enter into the bridge arms; consequently, it might be expected that the bridge balance, or a given unbalance reading, would tend to be more stable than the reference voltage measurements because the fluctuations of the polarization impedances have a negligible effect on the voltmeter reading. This is observed in practice. In addition, it is interesting to see that the bridge circuit is totally within the conducting fluid.

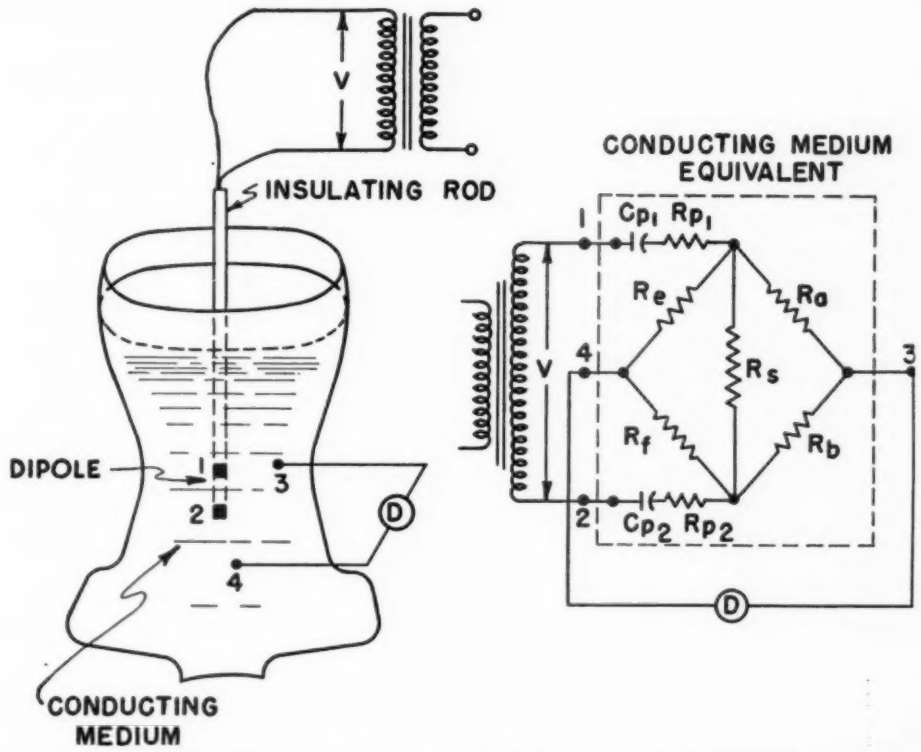

Fig. 7.—Bipolar measurements, illustrated on the left, are shown to be essentially bridge measurements in which the bridge arms do not contain the polarization impedances of the finite dipole. R_a, R_b, R_e, and R_f represent equivalent resistances from the liquid-side of the electrodes to the voltmeter *D* terminals.

Equivalent bridges provide a powerful tool for the analysis of experimentally observed effects. It can be seen, in terms of the bridge viewpoint, that the dipole system (in which only 1 per cent of the voltage applied to the dipole appears on the torso boundary) represents a bridge that is within approximately $\pm\frac{1}{2}$ per cent of balance for all measurements on the torso boundary, whether they be

unipolar or bipolar. This discloses and emphasizes the need for an exceptionally good bridge null to begin with if intelligible potential data are to be obtained on the boundary. The bridge viewpoint also explains why it is not possible to find two points on the torso boundary whose potential difference is less than a certain minimum without the addition of capacitance tuning. Moreover, in considering various systems for boundary-potential measurements it reveals which contain the dipole polarization impedances in the bridge arms and thereby enables a prediction of the general fluctuation behavior of the bridge null voltage, as well as indicating whether it is feasible to use large or small dipole currents.

While these observations and others make the equivalent bridge viewpoint worth while, it is important to remember that the system is basically a volume conductor involving spatial distributions of current and voltage in which the effects cannot always be viewed profitably from a lumped circuit point of view.

CENTER-ELECTRODE REFERENCE SYSTEM

It has been shown how the reference potential V_r can be established at the junction of two resistors, using a system which has the disadvantage of containing the electrode polarization impedances in the arms of the equivalent bridge. A reference-voltage system in which the polarization impedances do not appear in the arms of the equivalent bridge can be devised by introducing a third electrode C mounted rigidly between the two electrodes 1 and 2 of the finite dipole. The prime advantages of eliminating the polarization impedances from the bridge arms are that smaller finite dipoles, or larger dipole currents, or lower frequencies, can be used for a prescribed amount of fluctuation of the bridge balance. Moreover, the bridge can be balanced to better than 20,000:1 without the need of capacitance tuning, since the bridge is very nearly purely resistive. The physical construction of the third electrode can take several forms, such as a circular loop or a short straight wire as indicated in Fig. 8*a*. The reference electrode can be located at the potential V_r of Equation (1) by using a symmetrical, known-geometry system as mentioned previously. However, the center-electrode reference system is not satisfactory because of intolerable shifts of V_r owing to the influence of the medium boundary when the finite dipole is unsymmetrically located.

The inherent defect of this system was studied in terms of a spherical boundary which is amenable to theoretical analysis. When a finite dipole is located in a spherical system, no current lines pierce the equatorial plane containing the two electrodes and the sphere center. Therefore, half of the sphere may be removed without affecting the current or potential distribution in the other half (except for a factor of two which is easily accounted for).[7] This symmetry property enables experimental investigations with the use of a hemisphere, which is very convenient in permitting the equatorial plane containing the finite dipole to be probed, with minimum disturbance of the field. Despite the restriction that the potentials are not conveniently measurable inside the hemisphere, many properties of the spherical conducting system can be studied. A sketch of the

hemisphere apparatus and center-electrode reference system is given in Fig. 8 along with the equivalent bridge circuit, where the approximate delta-wye transformation of Fig. 5 has been incorporated.

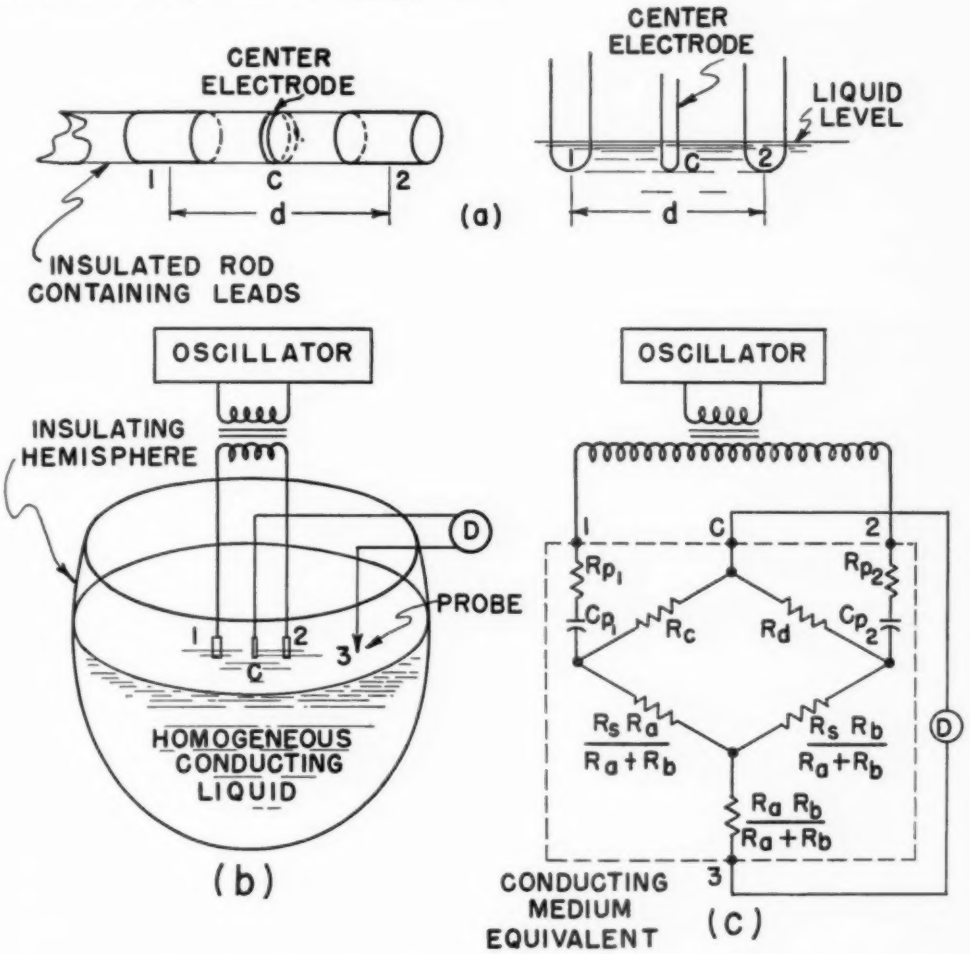

Fig. 8.—*a* shows two types of center-electrode designs, while *b* shows a finite dipole with center-electrode reference immersed in a hemisphere apparatus, the field of which is the same as that in half of a spherical medium; *c* gives the equivalent bridge circuit of the center-electrode reference system.

In order to locate the center-electrode C at the position where its potential is V_r, the finite dipole can be accurately centered in the hemisphere, as shown in Fig. 9a. Then V_r is the equipotential which is the perpendicular bisector of the line joining the two current electrodes, 1 and 2. Electrode C can be positioned so that the reading on D is zero when the probe is located on this perpendicular bisector. If now the finite dipole position is shifted, such as shown in Fig. 9b, the voltmeter D will indicate the voltage between reference electrode C and any point in the medium where the probe 3 may be located. Unfortunately, however, the change in the finite dipole position is accompanied by a shift of the

equipotentials between the two electrodes of sufficient magnitude that the potential of the reference electrode C differs appreciably from V_r, even though the physical location of C relative to electrodes 1 and 2 has not changed. Hence, the voltage readings on D obtained with an eccentrically located finite dipole are not probe voltages with respect to V_r but rather with respect to some other equipotential which terminates on C in the unsymmetrical case.

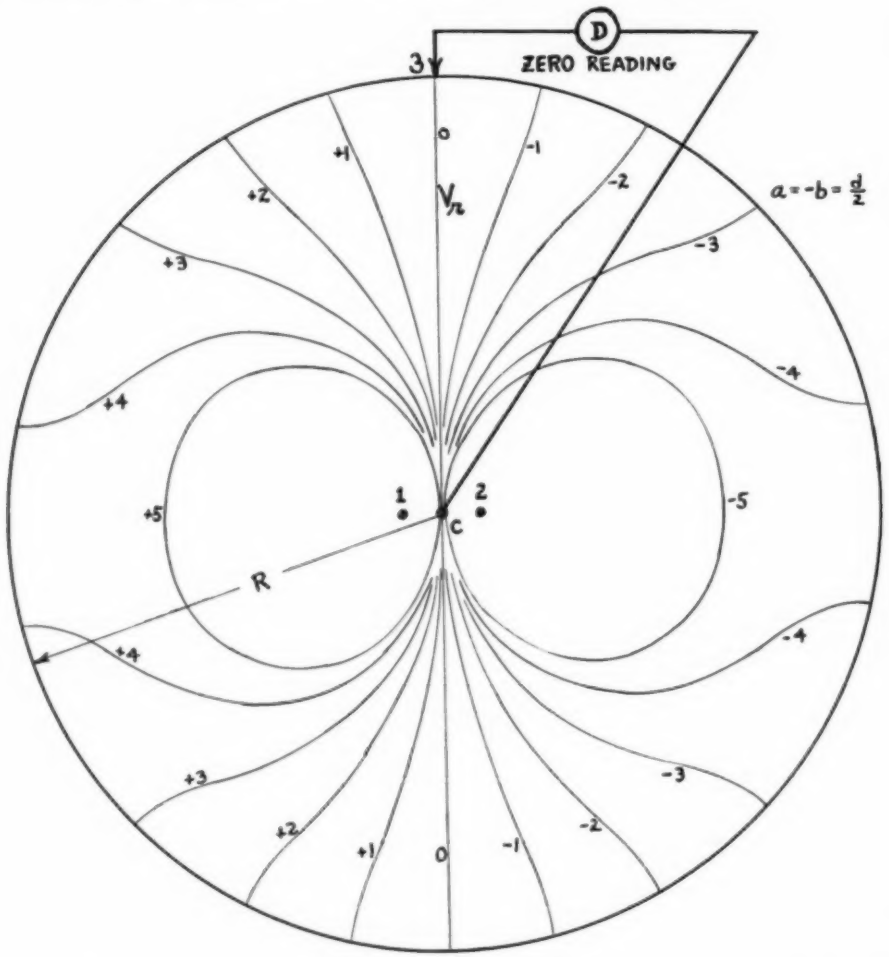

Fig. 9a.—Equipotentials in the equatorial plane of a spherical homogeneous conducting medium when the finite dipole is located in this plane. A centric finite dipole is shown in *a*.

It may seem surprising that the shift of equipotentials between the current electrodes, which is a region of very high field intensity, is appreciable when the boundary is relatively distant from the finite dipole. Indeed, the physical shift is very small but nevertheless too great to be tolerated if the 1 to 10 per cent accuracy requirements previously discussed are to be realized. The shift was studied experimentally for finite dipoles which were moved from the centric position of Fig. 9a along the line joining the two current electrodes. An equation

giving the potential V in volts on the equatorial plane for an eccentrically located finite dipole when the line passing through the current electrodes also passes through the center of the sphere is

$$V = \frac{I\rho}{4\pi} \sum_{n=1}^{\infty} (b^n - a^n) \left(\frac{n+1}{n} \frac{r^n}{R^{2n+1}} + \frac{1}{r^{n+1}} \right) P_n (\cos \Theta) \quad . \tag{4}$$

This equation is derived in Appendix I. The distance between the current electrodes is $d = b - a$; I is the finite dipole current; ρ is the resistivity of the homogeneous medium; R is the sphere radius; r is the distance from the sphere origin to any point where the potential is V; Θ is the angle between r and the finite dipole axis; $P_n(\cos\Theta)$ is the Legendre polynomial of order n; b and a are the distances from the origin of the two electrodes. The infinite series, Equation (4), converges only for r greater than $b > a$.

The potential at the boundary of the sphere is of particular interest and can be obtained from Equation (4) by imposing the condition $r = R$.

$$V_B = \frac{I\rho}{4\pi} \sum_{n=1}^{\infty} (b^n - a^n) \left(\frac{2n+1}{n} \right) \frac{1}{R^{n+1}} P_n (\cos \Theta) \quad . \tag{5}$$

An example of how this equation was used in the present study will now be given. Consider the case of an eccentric finite dipole for which $a = d$ and $b = 2d$. Equation (5) then becomes

$$V_B \Big]_{\substack{a=d \\ b=2d}} = \frac{I\rho}{4\pi R} \sum_{n=1}^{\infty} (2^n - 1) \left(\frac{d}{R} \right)^n \left(\frac{2n+1}{n} \right) P_n (\cos \Theta) \quad . \tag{6}$$

This potential is zero at $\Theta = \pm 77.5°$ as can be found from direct calculation using the experimentally employed value $\frac{d}{R} = 0.173$. A fixed reference probe was, therefore, placed at 77.5° and bipolar measurements were performed, measuring the potential between a movable probe with respect to the theoretically determined zero. Detailed plots showed that the equipotentials observed experimentally agreed to within several per cent or better of those predicted by Equation (6) for the boundary and by Equation (4) with $a = d$ and $b = 2d$ for points not on the boundary. In this way an electrode that was known to be at the potential V_r was established for this special case. Then the center-electrode potential (correctly set up in the centric case) was measured with respect to the boundary reference probe which was known to be at potential $V_r = 0$. For the eccentric case discussed here, the difference between the potential of the center electrode and V_r was approximately 15 per cent of the maximum boundary voltage of the centric case. Since only 1 per cent is tolerable, it is clear that the center-electrode system is not feasible. Moreover, the ratio $\frac{d}{R} = 0.173$ for this test reveals that the eccentricity was really not very great; i.e., the finite dipole is still roughly in the center of the medium (see Fig. 9b). Even worse departures of electrode C potential from V_r are encountered with greater eccentricity of the kind that might be required to cover the complete range of human hearts.

The physical displacement of V_r from the mid-point between the finite dipole to its altered position in the eccentric case can be estimated from a theoretical analysis of the potential gradient between two nearly spherical electrodes in an infinite medium. Such an analysis is given in Appendix II where it is shown that the potential between such electrodes along the line through their centers is given by

$$V \doteq \frac{2I\rho}{\pi} \frac{x}{d^2 - 4x^2}, \quad x < \frac{d}{2} \tag{7}$$

where V is the potential in volts at a point x measured from the mid-point between the two electrodes which are spaced a distance d apart. The electrode current is I and the resistivity of the homogeneous medium is ρ. The potential gradient at $x = 0$ is

$$\frac{\partial V}{\partial x}\Big|_{x=0} = \frac{2I\rho}{\pi d^2} \tag{8}$$

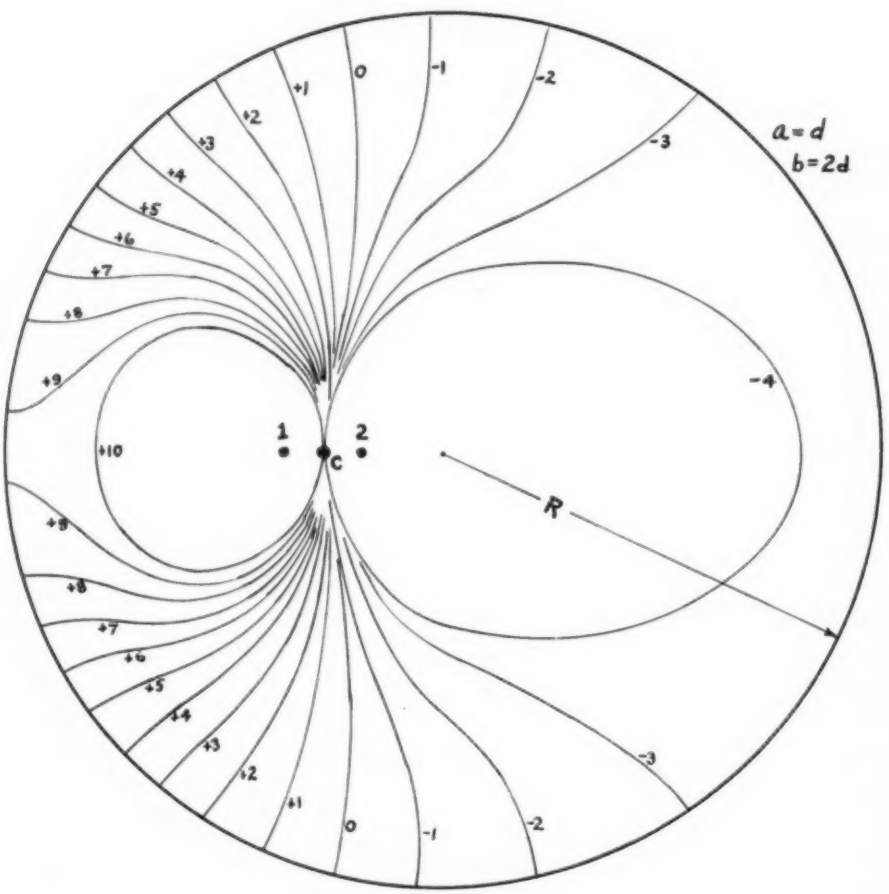

Fig. 9b.—Shows a case where the finite dipole has been shifted along its axis an amount 3d/2 from the centric case. d = 0.173 R.

and this is the approximate magnitude of the electric field intensity at the point where electrode C is located. The numerical value of this gradient for the case cited with an observed departure of V_r equal to 15 per cent of V_m is 45 mv./mm. This is obtained using $I = 2$ ma, $\rho = 2{,}200$ ohm-cm., $d = 2.5$ cm. The measured value of V_m was 30 mv. Therefore, the shift in electrode C potential was $0.15(30) = 4.5$ mv. which in the presence of a 45 mv./mm. potential gradient corresponds to a physical shift of 0.1 mm. Since $d = 25$ mm., this represents a shift of 0.4 per cent of the finite dipole spacing. The difficulties inherent in the reference voltage determination are well illustrated by this minute physical shift which causes electrical disturbances that are far outside the desired limits.

EXTERNAL REFERENCE SYSTEM

A practically feasible reference potential system can be devised using, in principle, the system of Fig. 3 which has the equivalent bridge circuit in Fig. 4. However, the practical difficulties attending this system are considerable, as discussed below.

A complete system is shown in Fig. 10. This is essentially the same as given in Fig. 3 except for the inclusion of electrical shielding throughout and the addition of the two capacitors C_1 and C_2 which are necessary to achieve the desired bridge balance in the presence of appreciable polarization impedance in the bridge arms.

It is desirable to operate at low dipole current in order to reduce the fluctuations in the polarization impedances and also to minimize I^2R heating of the conducting medium, the resistivity of the medium being temperature sensitive (of the order of 2 per cent per degree centigrade). Rough calculations, based on a bridge sensitivity of one part in 20,000, of permissible differential changes in medium resistivity indicate that unsymmetrical temperature differences in the medium of the order of 1/100°C can cause bothersome bridge-null instability. Dipole currents in the order of 10 to 20 microamperes are satisfactory from the standpoint of thermal gradients, but the boundary voltages produced on the model are then completely overriden by stray pickup unless the model is placed in a shield cage as indicated in Fig. 10. The 60 cycles per second pickup in the model is also large in comparison with the model boundary voltage but can be rejected by using a very narrow-band frequency-selective detector. A harmonic wave analyzer is used for this purpose, which also eliminates harmonics of the signal frequency.

In practice a compromise must be made among many factors in arriving at a workable system, some of which are: accuracy, size of finite dipole, oscillator frequency. As the electrode area of the finite dipole is reduced, maintaining constant dipole current, the attainable accuracy is also reduced because of bridge-null instability brought about by fluctuations of polarization impedance, the electrode current density having become greater. These fluctuations can be reduced by increasing the oscillator frequency, which brings about a reduction of the polarization impedances, but there is an upper limit beyond which it is undesirable to go because of the increased effects of stray capacitance in the bridge circuit and system-shielding difficulties.. The compromise that is reached varies with the

application; a typical set of practically useful parameters has been the use of platinum electrodes of approximate area 4 cm.^{2} operated at low current and platinized, which results in a stable bridge-null of about 1/20,000 of V at a frequency of 1 kc./sec. The fluctuations in the bridge-null arise from both thermal gradients in the medium and polarization impedance variations under these conditions.

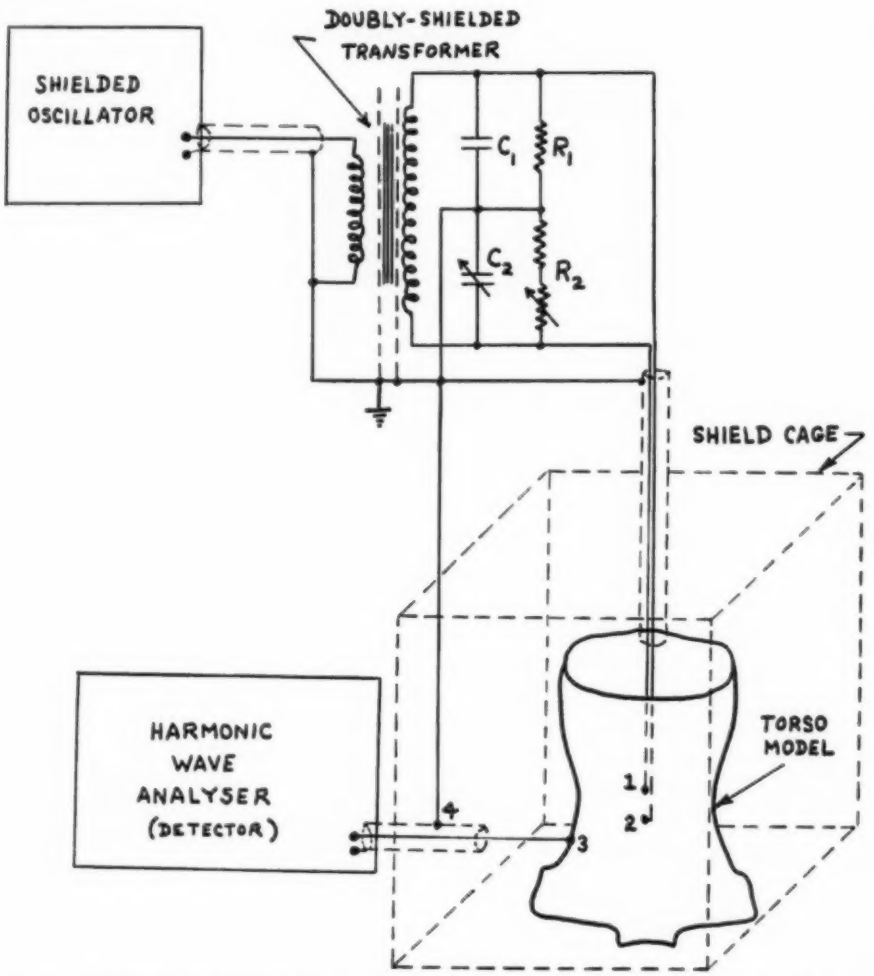

Fig. 10.—Practical arrangement for an external reference system which includes shielding, tuning capacitors in the bridge circuit, and a frequency-selective bridge detector. The oscillator is a Hewlett-Packard Low-frequency Oscillator, Model 202B; the detector is a Hewlett-Packard Harmonic Wave Analyzer, Model 300A; the bridge transformer is a General Radio Type 578-A. A Hewlett-Packard Amplifier, Model 450A, is used ahead of the detector when extremely small dipole currents are used.

Although the resistivity of the medium affects the performance of this system by altering the polarization impedance at the electrode interface, it is not a very pronounced effect provided the polarization impedance is small compared with the solution resistance. The main reason for this is that the boundary voltage is proportional to the voltage applied to the bridge independent, to first order, of the resistivity of the medium, as indicated by Equation (3).

SUMMARY

1. Measurements of potentials produced by a finite dipole immersed in an insulating torso model filled with a homogeneous conducting fluid are discussed.

2. The need for a reference potential is presented as well as a discussion of the accuracy with which the reference potential must be determined.

3. The equivalent bridge viewpoint is introduced and is shown to give considerable insight into the electrical nature of both unipolar and bipolar measurements.

4. A center-electrode reference system is described which has several advantageous features. The inherent defect of this system, a shift of equipotentials between the two current electrodes owing to the distant boundary, is pointed out and analyzed.

5. The experimental difficulties and interrelationship of the more important design factors of a practical reference potential system are presented.

The authors express appreciation to Dr. Herman Schwan for his helpful comments and discussions concerning polarization phenomena and to Dr. S. Reid Warren, Jr., and Mr. Albrecht J. Neumann for their many helpful suggestions.

APPENDIX I

The electric potential is desired in a homogeneous conducting medium bounded by a perfectly insulating spherical shell produced by a finite dipole of separation d and current I when the finite dipole is located in an equatorial plane of the sphere and when the line joining the two current electrodes passes through the center of the sphere.

First, the solution for the case of a finite dipole which has one electrode at the sphere center can be obtained. By linear superposition a pair of such finite dipoles can then be combined so that the poles at the origin annul one another, leaving the desired solution. Potentials in a homogeneous medium satisfy Laplace's equation

$$\nabla^2 V = 0 = \frac{\partial}{\partial r}\left(r^2 \frac{\partial V}{\partial r}\right) + \frac{1}{\sin\,\theta}\,\frac{\partial}{\partial \theta}\left(\sin\,\theta\,\frac{\partial V}{\partial \theta}\right) + \frac{1}{\sin^2\theta}\,\frac{\partial^2 V}{\partial \phi^2} \tag{9}$$

in which r, θ and ϕ are polar spherical coordinates. The boundary condition is $\partial V/\partial r = 0$ at $r = R$, the sphere radius; i.e., all current lines are tangential at the boundary. A second requirement is that as $R \to \infty$, V must reduce to the potential of a finite dipole field in a medium of infinite extent. In addition, the symmetry condition $\partial V/\partial \phi = 0$ is applicable.

The solution for $R \to \infty$ may be obtained readily since the potential V_∞ in this case is given by the elementary relation[8]

$$V_\infty = \frac{I\rho}{4\pi}\left(\frac{1}{r_1} - \frac{1}{r}\right) \tag{10}$$

where ρ is the resistivity of the medium and r_1 is the distance from the positive current source, located along the z-axis, a distance d from the origin, to the field point V_∞ and is given by[9]

$$\frac{1}{r_1} = (d^2 + r^2 - 2dr\cos\theta)^{-\frac{1}{2}} = \frac{1}{r} + \frac{1}{r}\sum_{n=1}^{\infty}\left(\frac{d}{r}\right)^n P_n(\cos\theta) \tag{11}$$

which converges for $r > d$. Hence, from Equation (10)

$$V_\infty = \frac{I\rho}{4\pi}\sum_{n=1}^{\infty}\frac{d^n}{r^{n+1}} P_n(\cos\theta) \quad . \tag{12}$$

Since the solution of Equation (9) with $\partial^2 V/\partial\phi^2 = 0$ must reduce to Equation (12) as $R \to \infty$, it appears that the form of V is

$$V = \sum_{n=1}^{\infty} \left(A_n r^n + \frac{B_n}{r^{n+1}} \right) P_n (\cos \Theta) \tag{13}$$

which is known to satisfy Equation (9) for any values of the constants A_n and B_n. A connection between A_n and B_n is obtained by imposing the boundary condition

$$\left.\frac{\partial V}{\partial r}\right]_{r=R} = 0 = \sum_{n=1}^{\infty} \left[n A_n R^{n-1} - (n+1)\, B_n\, R^{-n-2} \right] P_n (\cos \Theta) \tag{14}$$

which must hold for all Θ. Consequently, $A_n = (n+1)\, B_n / n R^{2n+1}$ which when inserted into Equation (13) yields

$$V = \sum_{n=1}^{\infty} B_n \left(\frac{n+1}{n} \frac{r^n}{R^{2n+1}} + \frac{1}{r^{n+1}} \right) P_n (\cos \Theta) \tag{15}$$

Since the constants B_n are independent of R, any convenient value of R may be used to evaluate them. Selecting $R >> r$, and comparing with Equation (12), it can be seen that $B_n = I\rho d^n/4\pi$. Hence, the solution which satisfies Laplace's equation, the boundary and symmetry conditions, and which also reduces to Equation (12) as $R \to \infty$, is

$$V = \frac{I\rho}{4\pi} \sum_{n=1}^{\infty} \left(\frac{n+1}{n} \frac{d^n r^n}{R^{2n+1}} + \frac{d^n}{r^{n+1}} \right) P_n (\cos \Theta) \tag{16}$$

Now superimpose two solutions of the form Equation (16); V_1 the potential due to a finite dipole of spacing b with a negative current source at the origin, and V_2 the potential due to a finite dipole of spacing $a < b$, with a positive current source of equal magnitude at the origin. The two electrodes which are not at the origin are each located on the z-axis.

$$V_1 = \frac{I\rho}{4\pi} \sum_{n=1}^{\infty} b^n \left(\frac{n+1}{n} \frac{r^n}{R^{2n+1}} + \frac{1}{r^{n+1}} \right) P_n (\cos \Theta) \tag{17}$$

$$V_2 = \frac{-I\rho}{4\pi} \sum_{n=1}^{\infty} a^n \left(\frac{n+1}{n} \frac{r^n}{R^{2n+1}} + \frac{1}{r^{n+1}} \right) P_n (\cos \Theta) \tag{18}$$

The resulting finite dipole has no source or sink at the origin, due to cancellation, and has a separation $d = b - a$, with potential given by

$$V = V_1 + V_2 = \frac{I\rho}{4\pi} \sum_{n=1}^{\infty} (b^n - a^n) \left(\frac{n+1}{n} \frac{r^n}{R^{2n+1}} + \frac{1}{r^{n+1}} \right) P_n (\cos \Theta) \tag{19}$$

which is the desired result[10] and Equation (4) of the text. The convergence condition of Equation (11) becomes, when applied to Equation (19), $r > b$.

APPENDIX II

The potential between two nearly spherical electrodes in an infinite homogeneous medium of resistivity ρ is desired. This potential may be obtained from the formula for a finite dipole in an infinite medium by letting the electrodes coincide with one of the equipotential surfaces around each infinitesimal pole. If the ratio of electrode diameter to spacing is reasonably small, it will be shown that the electrode shape is very nearly spherical.

Consider a positive point current source of strength I located in the xy-plane at x= s, y = 0, and a negative point current source of strength −I symmetrically located at x = −s, y = 0. Using Equation (10) the potential along the x-axis owing to these currents is given by

$$V = \frac{I\rho}{4\pi}\left(\frac{1}{s-x} - \frac{1}{s+x}\right) = \frac{I\rho}{2\pi}\,\frac{x}{s^2-x^2}, \quad x < s \tag{20}$$

$$V = \frac{I\rho}{4\pi}\left(\frac{1}{x-s} - \frac{1}{s+x}\right) = \frac{I\rho}{2\pi}\,\frac{s}{x^2-s^2}, \quad x > s \tag{21}$$

Define V_1 as the potential at any point x_1 on the x-axis such that $0 < x_1 < s$. Then directly from Equation (20)

$$V_1 = \frac{I\rho}{2\pi}\,\frac{x_1}{s^2-x_1^2} \tag{22}$$

Let x_2 be a point on the x-axis such that $x_2 > s$ and the potential is also V_1; then, using Equation (21)

$$V_1 = \frac{I\rho}{2\pi}\,\frac{s}{x_2^2-s^2} \tag{23}$$

Equating Equations (22) and (23)

$$x_2^2 = \frac{s^3 - sx_1^2 + s^2x_1}{x_1} \tag{24}$$

or defining k such that $x_1 = ks$ where $0 < k < 1$,

$$x_2 = s\left(1 + \frac{1}{k} - k\right)^{1/2} \tag{25}$$

Now let the positive electrode coincide with the surface of potential V_1, passing through x_1 and x_2. The distance spanned by this electrode along the positive x-axis is

$$d_e = x_2 - x_1 = s\left[\left(1 + \frac{1}{k} - k\right)^{1/2} - k\right] \tag{26}$$

Place the equal-size negative electrode symmetrically. Then the distance between the centers of the electrodes is

$$d = 2\left(\frac{x_1 + x_2}{2}\right) = s\left[\left(1 + \frac{1}{k} - k\right)^{1/2} + k\right] \tag{27}$$

A typical value of k encountered is 0.8 which corresponds to a ratio of electrode diameter to electrode spacing of approximately 0.2. With k = 0.8 Equations (25) to (27) yield

$x_1 = 0.800\ s$ $\qquad$ $x_2 = 1.204\ s$
$d_e = 0.404\ s$ $\qquad$ $d = 2.004\ s$

Therefore, the electrodes are very nearly spherical since d/2 is very nearly equal to s, and $s - x_1$ is very nearly equal to $x_2 - s$. Consequently, s may be taken as d/2 where d is the distance between the centers of substantially spherical electrodes and the potential in between the electrodes is given by Equation (20) with s = d/2 or

$$V = \frac{I\rho}{2\pi}\,\frac{x}{\left(\frac{d}{2}\right)^2 - x^2} = \frac{2I\rho}{\pi}\,\frac{x}{d^2-4x^2}, \quad x < \frac{d}{2} \tag{28}$$

which is Equation (7) of the text.

REFERENCES

1. Jones, G., and Christian, S. M.: The Measurement of the Conductance of Electrolytes. VI. Galvanic Polarization by Alternating Current, J. Am. Chem. Soc. **57**:272, 1935.
2. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, Am. Heart J. **9**:447, 1934.
3. Kohlrausch, F.: Ueber platinirte Electroden und Widerstandsbestimmung, Annalen der Physik und Chemie **60**:315, 1897.
4. Neumann, A. J., Kay, C. F., Hafkenschiel, J. H., Jr., and Zinsser, H. F., Jr.: The Distribution of Electrical Forces From a Dipole in the Living Hearts of Experimental Animals. (To be published.)
5. Makar, R., Boothroyd, A. R., and Cherry, E. C.: An Electrolytic Tank for Exploring Potential Field Distributions, Nature **161**:845, 1948.
6. Everitt, W. L.: Communication Engineering, New York, 1937, McGraw-Hill Book Company.
7. Peirce, B. O.: Elements of the Theory of the Newtonian Potential Function, ed. 3, Boston, 1902, Ginn and Company, p. 243.
8. Schelkunoff, S. A.: Electromagnetic Waves, New York, 1943, D. Van Nostrand Company, Inc., p. 129.
9. Sternberg, W. J., and Smith, T. L.: The Theory of Potential and Spherical Harmonics, Toronto, 1946, University of Toronto Press, p. 88.
10. Frank, E.: Electric Potential Produced by Two Point Current Sources in a Homogeneous Conducting Sphere, J. Appl. Physics **23**:1225, 1952.

ELECTROCARDIOGRAPHIC MANIFESTATIONS OF AIR IN THE CORONARY ARTERIES OF DYING AND RESUSCITATED HEARTS

THOMAS N. JAMES, M.D., THOMAS GEOGHEGAN, M.D., AND CONRAD R. LAM, M.D.

DETROIT, MICH.

THE fate and consequences of intravascular air form a subject which has attracted medical attention and investigation since before 1830, when Cormack blew "the contents of his chest, twice filled" into the veins of a horse.[1] Within the last three decades the vast difference in the effect of air in the right side of the heart as compared to that in the left side has become apparent. Excepting the presence of shunts, venous air in small amounts is relatively innocuous. Although this is not true when a gas enters the left side of the heart, until recently the reason has been controversial. Present evidence favors occlusion of the coronary arteries as the mechanism by which death occurs in the latter example.[2,3]

Electrocardiograms taken during coronary artery occlusion by air are rare, both in the clinical and experimental literature. Durant[4] in 1935 and Cameron[5] in 1945, each reported single cases in which clinical findings favored the diagnosis of coronary occlusion by air; each case was a twenty-four-year-old white woman who was receiving artificial pneumothorax for pulmonary tuberculosis. Electrocardiograms made in each case exhibited evidence of acute myocardial infarction; in addition, Cameron's case had transient heart block. Numerous single cases and several reviews[6,7] of similar clinical experience during thoracotomy, pneumosalpingography, thoracentesis, etc., are available, but no electrocardiograms are presented.

Durant and co-workers[8] in 1949 conducted experimental studies of the effect of air in the left side of the heart, focusing attention on the electrocardiographic changes. Eighteen procedures were performed on sixteen dogs. The procedures were of two types: fourteen times air was injected directly into the anterior descending coronary artery, four times into the left auricle or one of the pulmonary veins. In eight of the procedures a prolongation of the QRS complex was noted. Injury currents were reported in only twelve procedures, although "ischemic areas were induced within the myocardium in all the experiments." Four examples of various auriculoventricular conduction disturbances were observed. No attempt to resuscitate the animals was made.

The problem of air entering the coronary arteries during left cardiotomy has become vitally important with the newer methods of cardiac surgery. Heretofore

This work was supported by a grant from the Michigan Heart Association.

From the Divisions of Cardiology and General Surgery of the Henry Ford Hospital, Detroit, Michigan.

Received for publication March 7, 1953.

such an event has been considered untreatable and usually fatal.[9] The magnitude of this problem has been well recognized by Martin and Essex[10] who stated: "all intracardiac procedures on the left side of the heart are liable to failure unless some means is obtained of precluding the entrance of air into the coronary vessels." The technique recently devised by Geoghegan and Lam[3] clears the coronary tree of such air, allowing resumption of normal coronary blood flow. Their development represents the first effective means of dealing with the problem of coronary air. This is a study of the electrocardiographic aspects of intracoronary air, untreated and treated.

DESCRIPTION OF EXPERIMENTS

Nine adult male mongrel dogs were used. Five of these were designated as controls, while resuscitation was employed in four. The details of the operative procedure have been described previously. The general features are as follows: After anesthetization with endotracheal oxygen and ether, left chest thoracotomy was performed with the animal in the right lateral position and long axis horizontal. Aortic pressure was obtained from a cannula within the arch of the aorta. 1.5 c.c. of air per kilogram was injected rapidly near the mid-portion of the left ventricle. The coronary arteries were immediately filled with air bubbles by the first few subsequent systoles,[11] and cardiac output failed so rapidly thereafter that a large portion of the injected air was trapped in the dilating left ventricle. At thirty seconds the remaining air was aspirated from the left ventricle in all nine dogs.

Electrocardiograms were made with a portable direct-writing machine connected in tandem with a multichannel oscillograph[12] which was recording the aortic pressure. The latter instrument produced a photographic record of simultaneous aortic pressure and electrocardiogram. At the same time a direct-written electrocardiogram was made almost continuously, since operation of the direct-writer did not necessitate simultaneous use of the oscillograph.

Prior to the procedure, control electrocardiograms consisting of the three standard extremity leads, plus augmented unipolar extremity leads were obtained. Direct epicardial leads were not attempted, in order to leave the heart free for observation and various procedures. For the continuous tracing Lead aV_R was chosen because it best depicted all three major components of the cardiac cycle: P wave, QRS complex, and T wave.

In the four treated dogs resuscitative measures were instituted about one minute after the injection of air. The aorta was occluded with a snare distal to the left subclavian artery one to two minutes after air injection. When the spontaneous contractions were insufficient to propel the air segments along within the coronary arteries, manual systole was employed. This was continued until all the coronary arteries were clear of air. The aortic snare was then gradually released from six to twelve minutes after air injection, concluding the experimental procedures.

Following recovery, the six leads used in the control electrocardiogram were repeated.

RESULTS

1. *General Sequence of Events.*—Within ten seconds after air was injected into the left ventricle, bubbles of air were visualized entering and almost immediately filling the left anterior descending coronary artery. In all cases an abrupt hypertension occurred, (Fig. 1) lasting approximately twenty seconds. We have observed a similar hypertension after air injection into various major systemic arteries. At the peak of blood pressure rise, air was seen in the anterior descending coronary artery (the major coronary artery readily visible in the surgical exposure), and simultaneously injury current appeared in the electrocardiogram. Thereafter, the aortic pressure progressively fell, reaching zero level in two to four minutes in the control dogs. Cardiac rate was not significantly altered. In none of the animals did the injury current per se persist more than one and one-half minutes.

Of the five control animals the ventricles exhibited barely visible contractions in four dogs for four to fifteen minutes after air injection. In one dog ventricular fibrillation occurred at seventeen minutes, while the auricles were observed to continue beating regularly for over one hour. In three dogs both the auricles and ventricles stopped beating at the same time, while in a fourth dog auricular activity continued forty-three minutes after the ventricles had come to standstill.

Left ventricular dilatation was observed in all of the animals. On examining the hearts post mortem, the entire coronary tree was seen filled with air.

Three of the four treated animals were successfully revived. In the failure the coronary arteries were successfully cleared of air and a normal sinus rhythm was established, but the contractions were too weak to sustain necessary aortic pressure. In the three dogs which recovered completely, manual systole was maintained for from seven to ten minutes, after which time all three had established a normal sinus rhythm with ventricular contractions producing normal aortic pressure.

2. *Electrical and Mechanical Dissociation in the Dying Heart.*—The independence of electrical and mechanical reactions in the heart has been described previously, the difference being analyzed in normal hearts.[13] In this study we observed gross discrepancy between mechanical and electrical events during malfunction.

Although an electrocardiographic injury current and a fall in aortic pressure appeared at the same time, the injury current soon reverted to normal while the aortic pressure continued to decline. Normal electrocardiographic inscriptions were apparent even when the aortic pressure had declined to zero and no aortic pressure complexes were visible (Fig. 2).

During the air aspiration procedure thirty seconds after injection of the air, a certain amount of manipulation of the heart was inevitable. The electrocardiogram changed considerably in amplitude during aspiration when cardiac position was altered, but duration and contour of the complexes did not (Fig. 1). As soon as the manipulation was completed and the heart restored to its original position, however, there was no more evidence of the injury current seen prior to the aspiration. The decline in aortic pressure progressed unabated all this time.

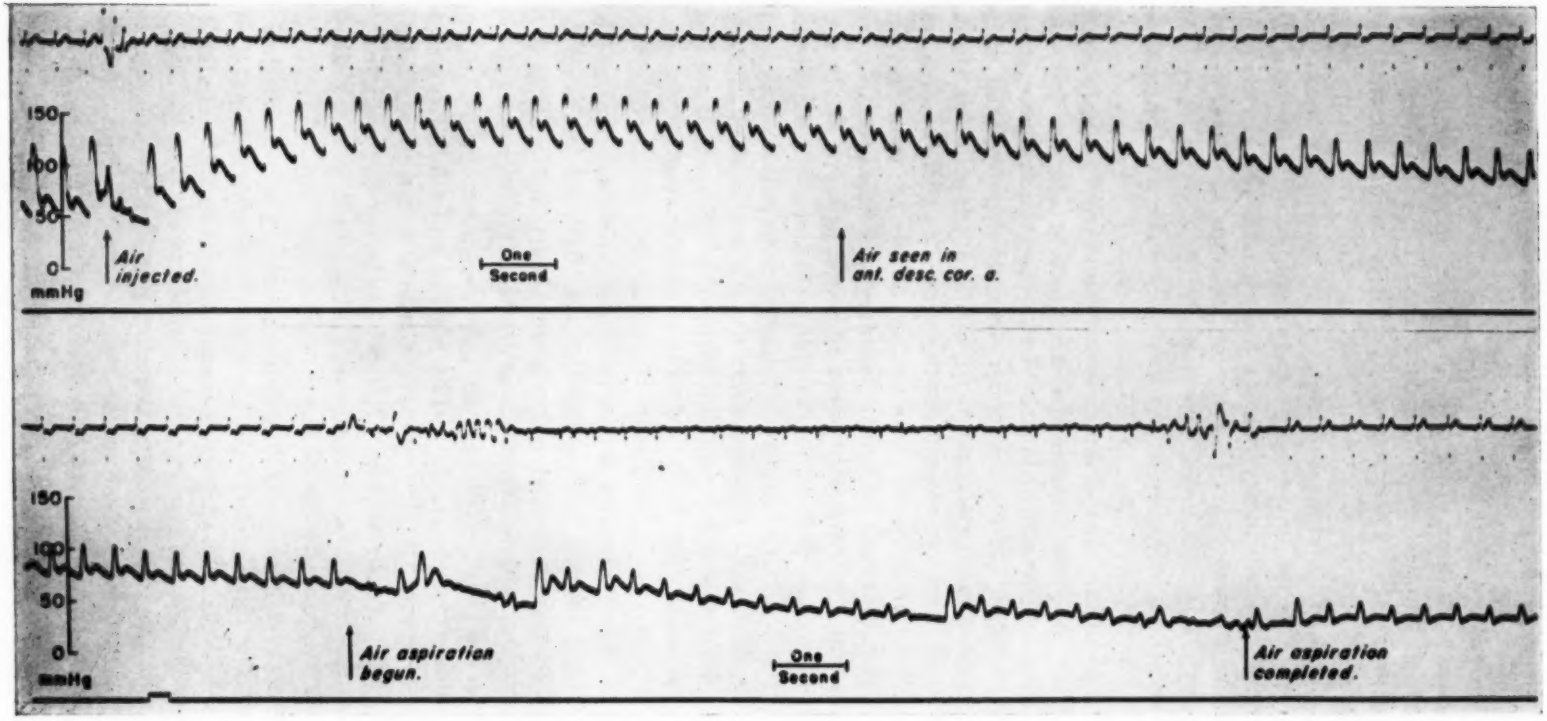

Fig. 1.—This is a bisected continuous strip of record during the early phases of a typical experiment. Of particular interest are the transient hypertension following air injection, the appearance of an injury current in the ECG as the aortic pressure falls, and the transient improvement noted in the latter portion following air aspiration. Unavoidable manipulation during air aspiration probably accounts for the temporarily normal appearance of the ECG. The upper tracing is the aV_R electrocardiogram; the lower is aortic pressure recorded from the aortic arch.

3. *Electrocardiograms of the Resuscitated Hearts.*—Initially the aortic pressure and electrocardiogram were the same in this group as in the control animals (Figs. 3, 4). An injury current was apparent within ten to twenty seconds after air injection, manipulation during air aspiration evoked transient electrocardiographic improvement while the aortic pressure continued to fall, and the general appearance of the heart deteriorated, as evidenced by dilatation and cyanosis.

After application of the aortic snare and institution of manual systole, neither the aortic pressure nor electrocardiogram reflected intrinsic cardiac activity.

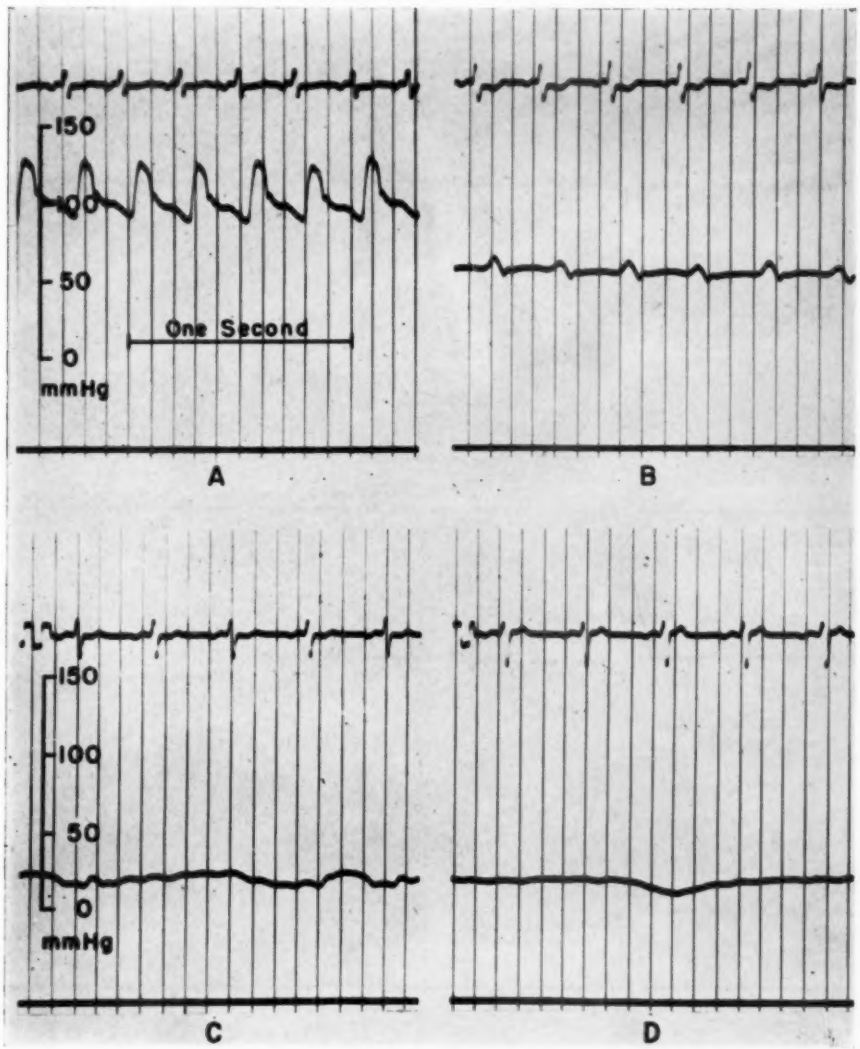

Fig. 2.—Upper tracing in each segment is the aV_R electrocardiogram; lower is aortic pressure. Segment *A* represents a control taken at 3:14 P.M.; *B* is at 3:15:20; *C* is at 3:16, and *D* at 3:16:30. Note progressive decline in aortic pressure as ECG assumes a more normal contour; variation in relation of amplitudes of R and S waves in ECG is due to change in axis of heart as ventricular dilatation occurs. The dip in segment *D* is a respiratory effect.

When the air segments had been pushed out of the visible coronary arteries, supraventricular complexes began to appear spontaneously in the electrocardiogram, although aortic pressure was usually still low. Manual systole was continued a few minutes after this phase, while the aortic snare was gradually being released. The supraventricular complexes progressively became the dominant ones, and aortic pressure improved until the heart was able to meet its own requirements in coronary circulation.

When the aortic pressure had returned to levels present prior to air injection, the electrocardiogram likewise was similar to that obtained prior to air injection (Figs. 3, 4).

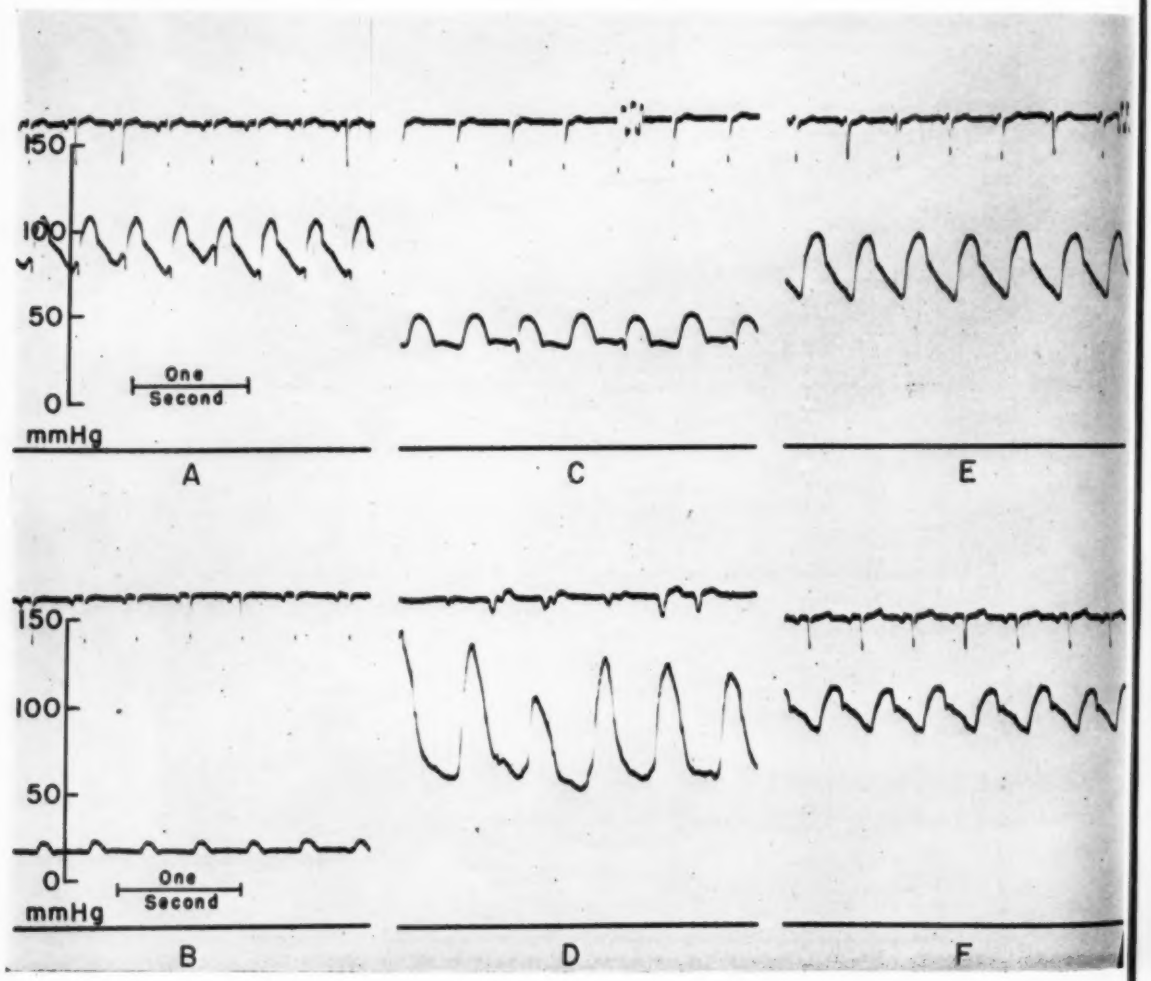

Fig. 3.—Six representative segments from the record of a typical treated dog. Segment *A* is a control taken at 3:41; *B* is at 3:45:25, air being injected at 3:45; *C* is at 3:50, after resuscitation had been proceeding for four minutes; *D* is at 3:51, during further cardiac massage; *E* is at 3:52, at which time gradual release of the aortic snare is about one-half complete, and *F* is at 4:05, twenty minutes after air injection. Note complete recovery in comparison to control tracing. Upper tracing is aV_R electrocardiogram, lower one is aortic pressure.

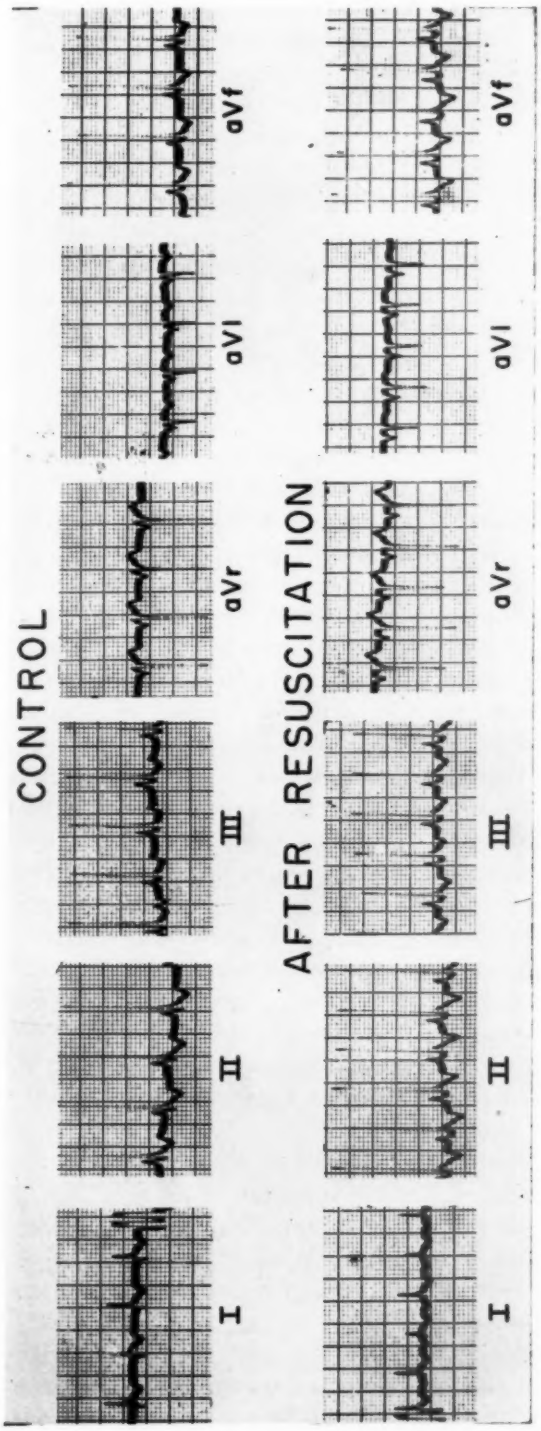

Fig. 4.—A comparison of all six leads of the electrocardiograms made before air injection and approximately thirty minutes later, following resuscitation. The second group reveals no residual evidence of injury.

4. *Auricular Complexes.*—Since the first dog developed ventricular fibrillation, the auricular complexes were obscured on the electrocardiogram by the fibrillation waves, although the auricles were observed to continue beating regularly. The second, third, and fourth control dogs manifested simultaneous auricular and ventricular standstill. The auricular complexes in those dogs were not remarkable.

After the ventricles ceased beating at approximately seven minutes after the injection of air in the fifth control dog, the auricles continued to inscribe P waves for almost an hour (Fig. 5). These isolated P waves retained their original contour initially but began to vary slightly in rhythm, much as is seen in sinus arrhythmia. One minute later, the general contour of the P waves began to vary in an irregular fashion. Three minutes after the cessation of ventricular activity it was observed that the left and right auricles were beating in grossly different rhythms, each regular in its own pace (Fig. 5,*A*). Three minutes later (thirteen minutes after the injection of air) the left auricle had gradually ceased beating and the only portion of the right auricle visibly contracting was the tip of the right auricular appendage; distinct P waves were still being inscribed (Fig. 5,*B*). Soon a second peak appeared on the P wave, representing an auricular T wave (Fig. 5,*B*,*C*).[14,15] The valley between these two peaks gradually became elevated, assuming the contour described by Hellerstein[16] and others,[17,18] as characteristic of auricular infarction and designated by them as elevated "P-T_a" segment (Fig. 5,*D*,*E*). Auricular fibrillation did not spontaneously develop.

5. *Conduction Disturbances Encountered.*—Arrhythmias of various sorts were seen in the five control animals (Fig. 6). Generally, as the degree of anoxia increased the following sequence was manifest. Partial auriculoventricular dissociation appeared, gradually increasing in degree until complete dissociation was present; shortly thereafter, the ventricles usually ceased beating. Regular auricular beats continued for approximately one hour. The phenomenon of long-persistent auricular activity following complete ventricular standstill has since been observed in a number of dogs not included in this report.

Several manifestations of auriculoventricular nodal anoxia were observed. The first four control dogs all developed reciprocal beating (Pick and Langendorf's[19] "re-entry phenomenon") in from one to two minutes after air injection (Fig. 6,*C*,*D*); the fifth dog's electrocardiogram was also suggestive of this phenomenon but not conclusive. The treated animals showed no arrhythmias prior to the institution of resuscitative measures.

Wenckebach's phenomenon occurred in the second and third control dogs approximately two minutes after the injection of air (Fig. 6,*A*,*B*).

In the fourth resuscitated dog, approximately seven minutes after air injection and with release of aortic snare about one-half completed, a peculiar shortening of the P-R interval with a regular ventricular response was observed, the first portion of which is reproduced in Fig. 5,*E*. While the Q-Q interval remained constant, the P wave not only migrated toward the QRS but through it, appearing on the other side superimposed on the ascending limb of the S wave. Shortly thereafter a sinus rhythm gradually reappeared; the contour of the QRS complex remained unaltered. The entire period of migration occupied no more than one minute and did not reappear.

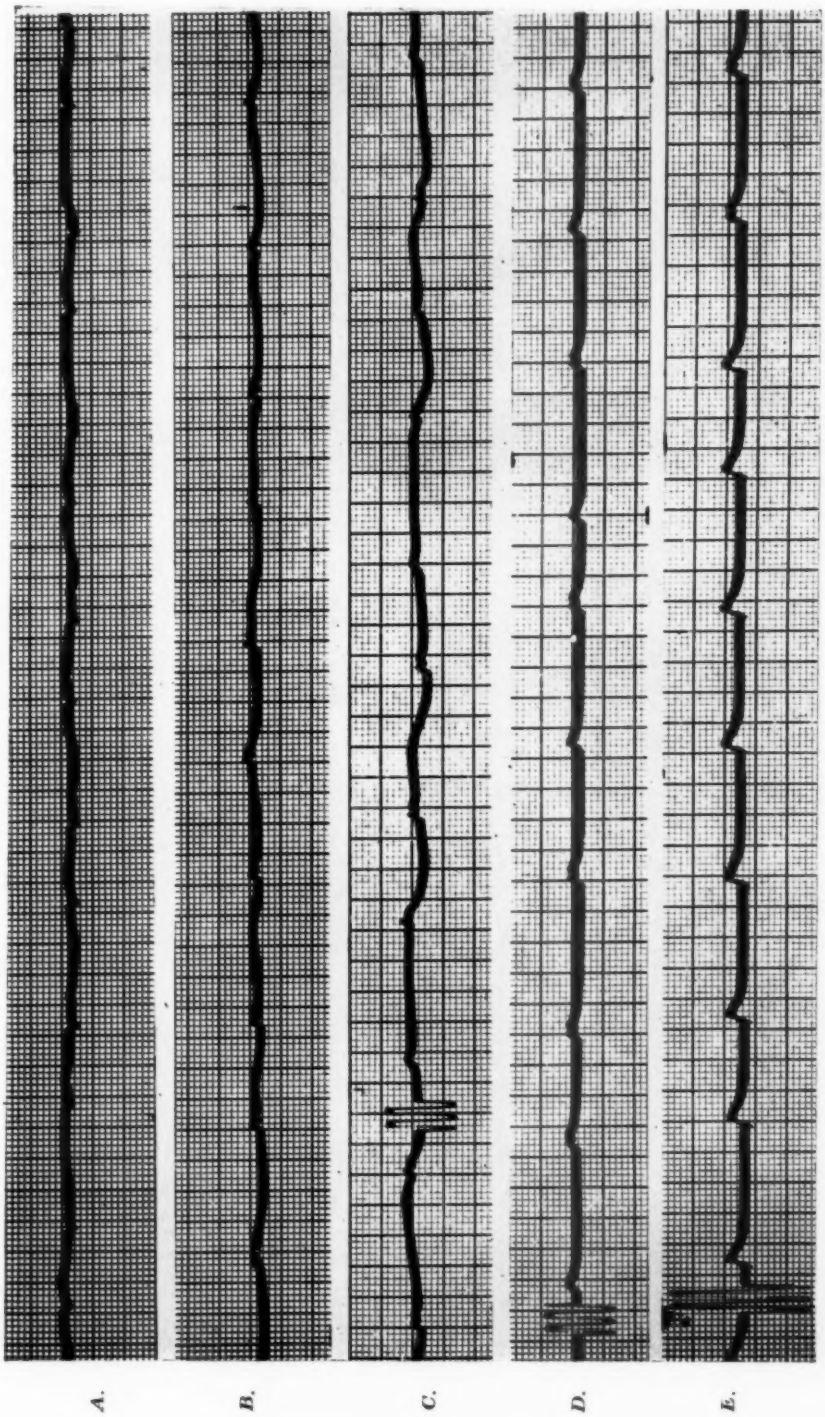

Fig. 5.—Auricular complexes recorded after ventricular standstill in the fifth control dog: aV_R electrocardiogram. See text for explanation. Note standardization difference in segments *D* and *E*; both were recorded at approximately the same time, but the latter at an increased sensitivity of the galvanometer string.

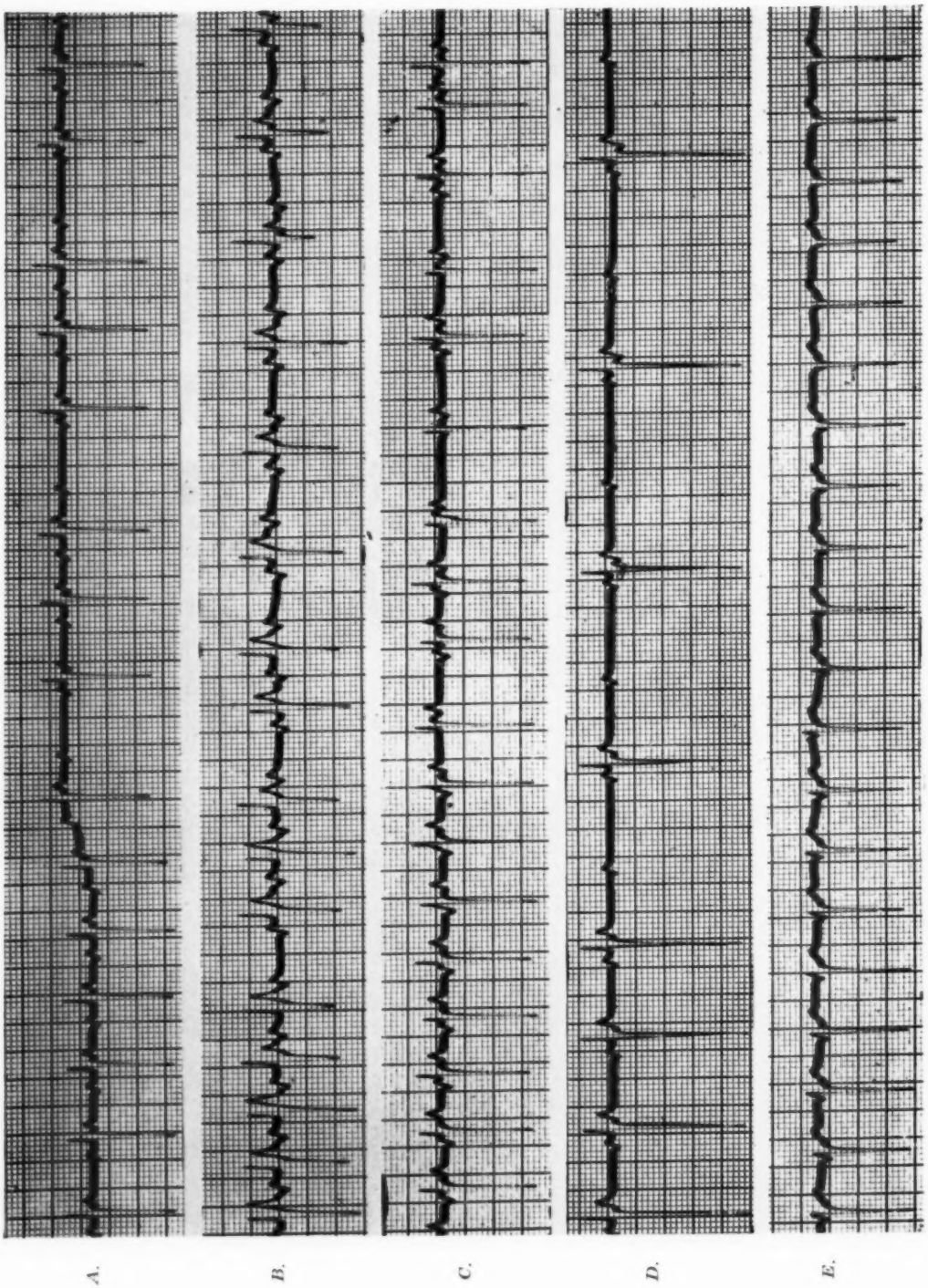

Fig. 6.—Supraventricular arrhythmias encountered during coronary artery occlusion by air. See text for explanation. All segments are aVR leads.

6. *Miscellaneous Observations.*—During massage of the heart while the aorta was clamped, simultaneous recordings of aortic pressure and the aV_R electrocardiogram were made. Handling the heart produced numerous ventricular extrasystoles of multicentric origin (Fig. 7,*B*). In addition, however, auricular fibrillation occurred paroxysmally (Fig. 7,*A*).

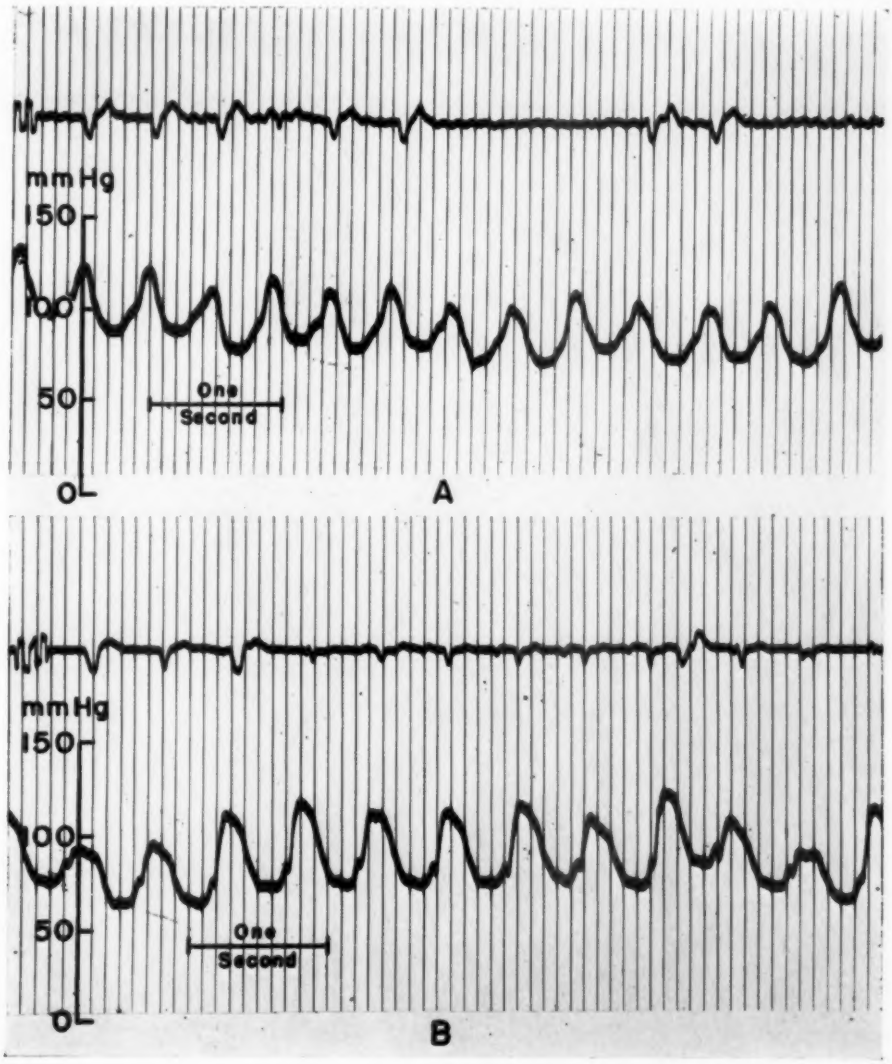

Fig. 7.—Simultaneous tracings of aV_R electrocardiogram and aortic pressure during cardiac massage. See text for explanation.

Fig. 6.—Supraventricular arrhythmias encountered during coronary artery occlusion by air. See text for explanation. All segments are aV_R leads.

In the fourth treated animal a rise in the aortic pressure appeared spontaneously (Fig. 8). At this time the aortic snare was about three-fourths open, and opening had been gradually carried out for the preceding two minutes. The etiology of this spontaneous hypertension is not clear. It was accompanied by a tachycardia, sudden marked S-T segment depression, and a bright pinking of the

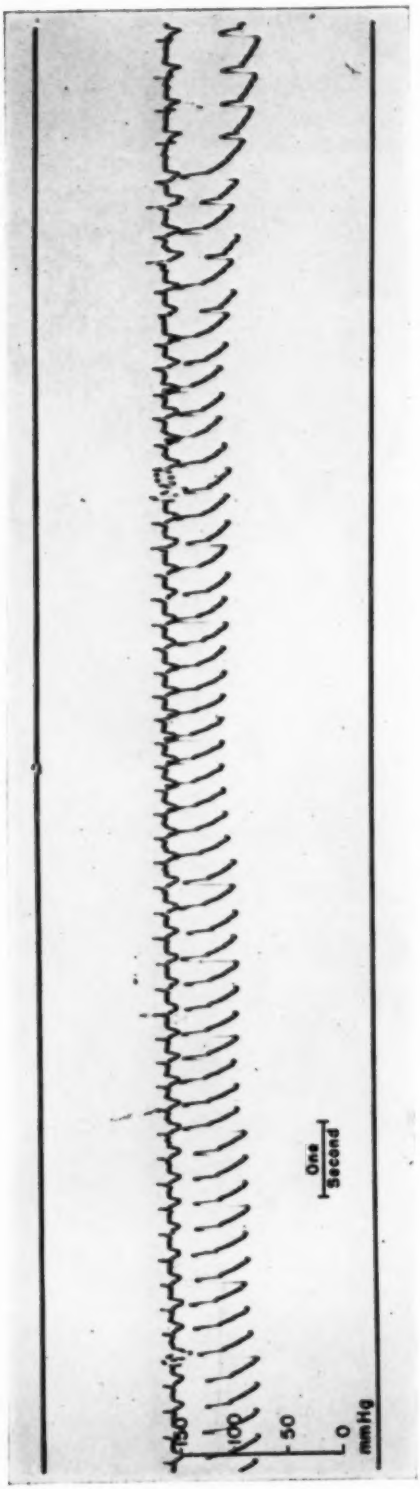

Fig. 8.—Simultaneous tracings of aV_R electrocardiogram and aortic pressure in the fourth treated dog at a time when the aortic snare was about three-quarters open. See text for explanation.

myocardium; neither the hypertension nor the associated changes were long sustained. This phenomenon was noted in previous experiments after release of aortic constriction in which no electrocardiograms were taken. It bears a resemblance to a similar response occurring after release of caval occlusion and suggested by Dryer to Bailey and co-workers[20] to be due to release of epinephrine.

COMMENT

In view of the appearance of various injury currents synchronous with the visualization of air bubbles in the anterior descending coronary artery, it is reasonable to presume that the net effects were the same as those seen following any type of occlusion of this artery. This is in agreement with the findings of Durant when he injected air directly into this artery.[8]

It is more difficult to explain the subsidence of the injury current while the hearts were obviously dying. Since an injury current occurs usually during imbalance in oxygenation of various portions of the myocardium, it is conceivable that this imbalance is extinguished when all the coronary arteries are filled with air and consequently occluded, rendering the entire myocardium totally and equally anoxic.

The effect of anoxia upon the auriculoventricular node varied from animal to animal and also in the same animal as the anoxia increased. Some of the early manifestations are illustrated in Fig. 6, but as the anoxia became more severe, increasing auriculo-ventricular dissociation was the rule.

Why the auricular T wave and the elevated P-T_a segment were so tardy in appearing is open to speculation.

SUMMARY AND CONCLUSIONS

Injection of lethal amounts of air into the left ventricular cavity is followed by occlusion of the coronary arteries by this air. The electrocardiogram initially manifests an injury current following this occlusion but soon reverts to a nonpathologic contour. During this phase there is gross dissociation between the mechanical and electrical activity of the heart. As the anoxia progresses, various conduction disturbances appear. Ventricular fibrillation is uncommon.

The changes produced by air in the coronary arteries are entirely reversible, with the recovered animal exhibiting no electrocardiographic evidence of residual injury to the heart.

We are grateful to Dr. F. Janney Smith for his kind suggestions in the preparation of this report.

REFERENCES

1. Cormack, J. R.: Quoted by Hare, H. A.: The Effect of the Entrance of Air Into the Circulation, Therapeutic Gazette, Third Series, **5**:606, 1889.
2. Moore, R. M., and Braselton, C. W., Jr.: Injections of Air and of Carbon Dioxide Into a Pulmonary Vein, Ann. Surg. **112**:212, 1940.
3. Geoghegan, T., and Lam, C. R.: The Mechanism of Death From Intracardiac Air and Its Reversibility, Ann. Surg. (In press.)
4. Durant, T. M.: The Occurrence of Coronary Air Embolism in Artificial Pneumothorax, Ann. Int. Med. **8**:1625, 1935.

5. Cameron, D. R.: Transient Heart Block and Coronary Occlusion in Pleural Shock, Brit. Heart J. **7**:104, 1945.
6. Reyer, G. W., and Kohl, H. W.: Air Embolism Complicating Thoracic Surgery: Report of Ten Cases, J.A.M.A. **87**:1626, 1926.
7. Cohen, A. C., Glinsky, G. C., Martin, G. E., and Fetterhoff, K. I.: Air Embolism, Ann. Int. Med. **35**:779, 1951.
8. Durant, T. M., Oppenheimer, M. J., Webster, M. R., and Long, J.: Arterial Air Embolism, Am. Heart J. **38**:481, 1949.
9. Kent, E. M., and Blades, B.: Experimental Observations Upon Certain Intracranial Complications of Particular Interest to the Thoracic Surgeon, J. Thoracic Surg. **11**:434, 1942.
10. Martin, W. B., and Essex, H. E.: Experimental Production and Closure of Atrial Septal Defects With Observation of Physiologic Effects, Surgery **30**:283, 1951.
11. Gundermann, W.: Ueber Luftembolie. Mitteilungen aus den Grenzgebeiten der Medizin und Chirurgie **33**:261, 1921.
12. Schafer, P. W., and Shirer, H. W.: An Impedance Gauging System for Measurement of Biologic Pressure Variables, Surgery **26**:446, 1949.
13. Wiggers, C. J.: The Independence of Electrical and Mechanical Reactions in the Mammalian Heart, Am. Heart J. **1**:173, 1925.
14. Sprague, H. B., and White, P. D.: Clinical Observations on the T Wave of the Auricle Appearing in the Human Electrocardiogram, J. Clin. Investigation **1**:389, 1925.
15. Prinzmetal, M., Corday, E., Brill, I. C., Oblath, R. W., and Kruger, H. E.: Auricular Arrhythmias, Springfield, Ill., 1952, Charles C Thomas.
16. Hellerstein, H. K.: Atrial Infarction With Diagnostic Electrocardiographic Findings, Am. Heart J. **36**:422, 1946.
17. Sanders, A.: Experimental Localized Auricular Necrosis. An Electrocardiographic Study, Am. J. M. Sc. **198**:690, 1939.
18. Cushing, E. H., Feil, H. S., Stanton, E. J., and Wartman, W. B.: Infarction of the Cardiac Auricles (Atria): Clinical, Pathological and Experimental Studies, Brit. Heart J. **4**:17, 1942.
19. Pick, A., and Langendorf, R.: A Case of Reciprocal Beating With Evidence of Repetitive and Blocked Re-Entry of the Cardiac Impulse, Am. Heart J. **40**:13, 1950.
20. Cookson, B. A., Neptune, W. B., and Bailey, C. P.: Hypothermia as a Means of Performing Intracardiac Surgery Under Direct Vision, Dis. of Chest **22**:245, 1952.

STUDIES ON THE QRS-T ANGLE

ROBERT A. HELM, M.D., AND NOBLE O. FOWLER, JR., M.D.*

CINCINNATI, OHIO

THE purpose of this paper is to report some studies relating to the determination of the angle between certain spatial QRS and T vectors and the angles between their planar projections. These were based upon the following considerations.

1. Although the projections of QRS and T vectors have been depicted in the frontal plane, and the projected frontal QRS-T angle has been measured, the authors know of no description in the electrocardiographic literature of a method to calculate mathematically the angle between two spatial vectors, given only the angular positions of their projections on two separate and mutually perpendicular planes. Since it is more practical to measure the positions of vector projections on given planes than it is to determine vector positions in space, such a method of calculation assumes importance and will be given here.

2. Various spatial reference frames have been used to study the spatial electrical forces of the heart. Since there is no agreement as to the best reference frame for spatial vectorcardiography, it is evident that an extensive statistical study of the limits of normality of the angle between the largest spatial QRS and T vectors determined with any of the three-dimensional frames would be premature unless preliminary study demonstrates that results obtained with one method are interchangeable with those determined by another method. The latter possibility has been explored.

3. A method of calculating the angle between the mean spatial QRS and T vectors from a clinical scalar electrocardiogram, differing considerably in its details from Grant and Estes' method[1] of estimating this angle has been developed.

METHODS

Twenty subjects with normal hearts, as demonstrated by physical examination, thoracic teleroentgenogram, and electrocardiogram, were studied. Their ages ranged between 18 and 57 years with a mean of 32. Only one subject exceeded 50 years of age. Electrocardiograms, consisting of Leads I, II, III, aV_R, aV_L, aV_F and V_1 through V_6, were taken on all twenty subjects with a Sanborn Viso-Cardiette. Vectorcardiograms were obtained from fifteen of the twenty

From the Cardiac Laboratory, Cincinnati General Hospital and the Department of Internal Medicine, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

This study was carried out during the tenure (R.A.H.) of a Heart Traineeship sponsored by the National Heart Institute and during the tenure (N.O.F.) of a Research Fellowship sponsored by the American Heart Association.

*Present address: Noble O. Fowler, Jr., M.D., Cardiac Laboratory, The Brooklyn Hospital, DeKalb Avenue & Ashland Place, Brooklyn 1, New York.

Received for publication March 9, 1953.

subjects, utilizing the cube reference frame described by Grishman and his associates.[2] All three components were equally standardized. Vectorcardiograms were obtained from thirteen of the twenty subjects, utilizing the equilateral tetrahedral reference frame described by Wilson and his associates.[3] Standardization factors of 1.7 and 1.2 were used for the VF and VB components respectively. Nine of the twenty subjects had vectorcardiograms recorded with both the cube and tetrahedral systems.

The vectorcardiograms were recorded with the Technicon "Cardiograph" and the Technicon "Vectorscope." They were taken consecutively rather than simultaneously in the frontal, sagittal, and transverse planes. The polarities of the components of both reference frames were so selected that the recorded vectorcardiograms were viewed as follows: 1. Frontal plane: In an anterior-posterior direction with the subject upright. 2. Sagittal plane: In a right-left direction with the subject upright. 3. Transverse plane: In a head-foot direction with the subject prone.

We have arbitrarily measured in degrees the angular positions of vector projections on the various planes as follows: 1. Frontal plane: In a clockwise direction from the (patient's) left end of the horizontal axis (*x axis* in Fig. 1). 2. Sagittal plane: In a clockwise direction from the inferior end of the vertical axis (*y axis* in Fig. 1). 3. Transverse plane: In a clockwise direction from the posterior end of the anterior-posterior axis (*z axis* in Fig. 1). These angles are designated as $\propto xy$, $\propto yz$ and $\propto zx$ for the frontal, sagittal, and transverse planes respectively. When dealing with more than one vector a prime is added to the letters of the subscript to designate the second vector (e.g., $\propto x'y'$). Since this paper is concerned only with QRS and T vectors the prime is used for designation of the latter.

In measuring the angles of the projections of the largest QRS vector on the various planes of the vectorcardiograms, a line was drawn from the null point, corresponding to the isoelectric line of the electrocardiogram, to the most distal point of the QRS loop. The angle formed by this line and its intersection with any line parallel to the axis of reference is measured as has been described. The same technique, utilizing the null point and the most distal point of the T loop, was used to measure the angle of the projection of the largest T vector.

These measurements were made for all three planes of the vectorcardiograms when possible. However, it was repeatedly noted that the largest vector projection could be determined with more accuracy in certain planes than in others. For this reason the angular position of the vector projection in that plane in which the measurement was deemed least accurate was calculated from the angular positions measured in the other two planes by means of Equations (17), (18) and (19) given in the appendix. If the measurements were deemed inaccurate in two planes, the vectorcardiogram was discarded.

The determinations of the angular positions of the frontal plane projections of the mean QRS vector ($\propto$xy) and of the mean T vector ($\propto$x'y') were made from the transitional complexes of the standard and unipolar extremity leads of the electrocardiogram, according to the method of Grant and Estes[1] and Graettinger and associates.[4]

For determination of the mean QRS and T vector projections on the transverse plane, the precordial leads V_1 through V_6 were considered to lie in approximately the same plane. Since there is considerable disagreement, as judged by illustrations in various books and papers as to the positions of the precordial electrodes with reference to the electrical center of the heart and the horizontal and anterior-posterior axes of the body, we have used the angular positions shown

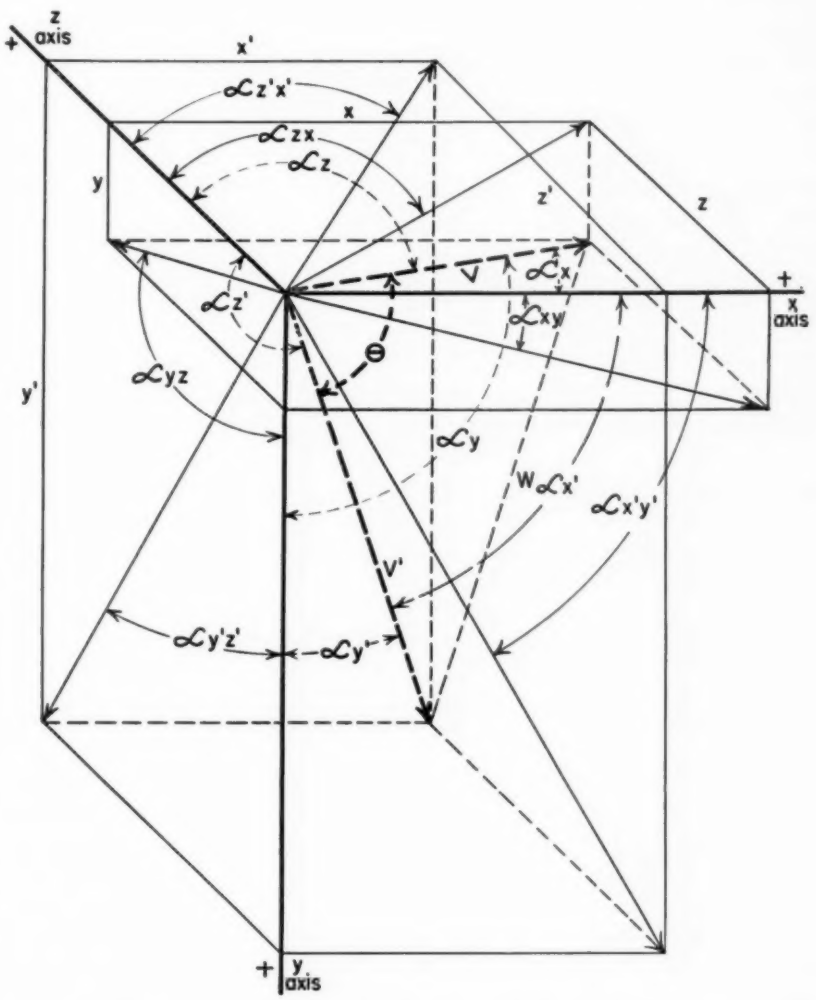

Fig. 1.—Diagram illustrating the designations of the angular measurements. See text.

in Fig. 2, constructed with the aid of a cross-sectional anatomical drawing,[5] at approximately the level of the precordial electrodes. The center point of the heart, *E*, lies to the left of, and anterior to, the center of the chest. Utilizing the transitional zone concept of Grant,[1,6,7] the angular positions of the projections of the mean QRS and T vectors on this plane were determined. Grant does not

assign an angular quantity to this estimation, but rather uses the transitional point together with the corresponding vector projection on the frontal plane to form a visual or actual three-dimensional model,[1,7] thus arriving at an estimate of the position of the vector in space. We have found it extremely difficult to make a quantitative determination of the spatial QRS-T angle by Grant's method. With the modification described above, however, it is relatively simple to assign a value to $\propto zx$ for the QRS and to $\propto z'x'$ for the T, these values together with those of the frontal plane being used for the calculation of the spatial angle.

The values for $\propto xy$, $\propto x'y'$, $\propto zx$ and $\propto z'x'$ were thus obtained for the largest QRS and T vectors with the cube and tetrahedral vectorcardiograms as well as for the mean QRS and T vectors with the 12 lead electrocardiograms. The angles between the frontal and transverse planar projections of the QRS and T vectors were then simply calculated as the angular differences between $\propto xy$ and $\propto x'y'$ and between $\propto zx$ and $\propto z'x'$, respectively. These frontal and transverse planar angles are designated, hereafter, as θxy and θzx respectively. The designation θ is given to the angle between the spatial QRS and T vectors. This angle was calculated by means of Equations (7), (10), (13) or (15), and (14), given in the appendix.

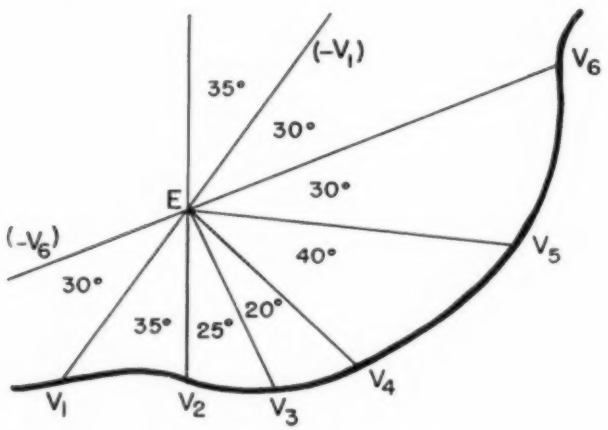

Fig. 2.—Diagram based upon a cross-section anatomical drawing, of the angular arrangement of the exploratory V lead electrodes about the center of the heart. See text.

RESULTS

The following means and standard deviations were obtained with the three reference frames used:

	VECG*	Cube	Tetrahedron
θ	43.4 ± 20.2	17.8 ± 10.5	27.7 ± 13.7
θxy	20.0 ± 15.6	13.8 ± 8.13	24.5 ± 13.7
θzx	51.0 ± 25.0	11.4 ± 11.2	16.2 ± 12.1

Each of the means differed significantly from zero ($P < .001$ in all instances).

(*See footnote on opposite page.)

The significance of the difference between two corresponding means was determined from Sukhatme's tables by means of the d test.[8] The following probabilities were obtained:

	VECG Cube	VECG Tetrahedron	Cube Tetrahedron
θ	$<.01$	$<.05$	.05
θxy	$>.05$	$>.05$	$<.05$
θzx	$<.01$	$<.01$	$>.05$

There was thus a significant difference between two corresponding means at or below the 5 per cent point in all but three instances.

Regression formulas[9] were applied in an attempt to demonstrate an association between corresponding QRS-T angles obtained with the three reference frames. An association of significance ($P < .05 > .02$) was found in only two instances: VECG and Cube θ and VECG and Tetrahedron θxy.

DISCUSSION

A trigonometric method has been developed to calculate mathematically the angle between two spatial vectors, given the angular positions of the vector projections on two mutually perpendicular planes. The end formulas and their derivations are given in the appendix.

Based upon a method of vector analysis of routinely recorded 12 lead electrocardiograms, the statement has been made that, in normal subjects of any age (excluding perhaps elderly subjects), the spatial angle formed by the mean QRS and T vectors is usually less than 40° and rarely exceeds 50°.[1] It is of interest, therefore, that in our group of twenty normal subjects vector analysis of 12 lead electrocardiograms by the method described herein has yielded spatial QRS-T angles exceeding 40° in eleven instances, 50° in five instances, 60° in four instances and 80° in two instances. The mean of the spatial QRS-T angles obtained with our VECG analysis of this small series is 43.4° with a standard deviation of 20.2°. It seems to us that the likely explanation for this discrepancy lies in the fact that the previous estimate, although based upon the same transitional zone technique, was not derived with the same application of trigonometric principles. However, it is possible that, if a diagram is substituted for our Fig. 2 so that the precordial electrode positions are grouped in a rather small area, values of decreased magnitude might be obtained for the spatial QRS-T angle. It should be emphasized, however, that this would not obtain if a transitional point for either QRS or T were located to the right beyond V_1 or to the left beyond V_6. In such circumstances a compact placement of points V_1 through V_6 would cause the QRS-T angle to have an increased value. Moreover, our Fig. 2 is similar to the

*The designation, VECG, is used to indicate the vector analysis of a 12 lead electrocardiogram as herein described. Since the areas of positive and negative deflections are used in determining the location of the transitional zones, this is a method of estimating the mean QRS and T vectors.[1] The analysis of the cube and tetrahedral vectorcardiograms by the method described yields an estimate of the largest QRS and T vectors. Although results obtained with the electrocardiographic analyses are therefore not strictly comparable to the results obtained with the vectorcardiographic measurements, it is felt that the comparison is of interest.

diagrams published by Duchosal and Grosgurin,[10] based upon their extensive anatomic and vectorcardiographic studies, and also shows a close resemblance to Simonson's recently published diagram,[11] derived from a cross-sectional anatomic drawing. It is our opinion, therefore, that the previously suggested limit of normality[1] for the spatial QRS-T angle, obtained by vector analysis of a routinely recorded 12 lead electrocardiogram, is too low. Langner[12] came to the same conclusion after vector analysis of a smaller selected group of electrocardiograms, using a geometric model to facilitate estimation of the spatial angle.

As mentioned in the introduction, there is little to justify an extensive analysis of the limits of normal for the angle between the largest spatial QRS and T vectors with any of the presently advocated vectorcardiographic spatial reference frames until one is generally accepted by all workers, a contingency which seems unlikely at the present time. Moreover, the statistical analysis of our small series obtained with two commonly used reference frames, the cube and equilateral tetrahedron, suggests that data pertaining to this angle obtained with one are not comparable with data obtained with the other.

There was no significant difference in the means of the angles between the transverse projections of the largest QRS and T vectors with the cube and tetrahedral frames (11.4° and 16.2° respectively). However, the mean of the angle between the transverse projections of the mean QRS and T vectors determined with vector electrocardiographic analyses was much larger (51°) and undoubtedly accounts for the relatively large spatial angle obtained with this method. Whether this marked discrepancy is due to fundamental defects in the method of vector analysis of the electrocardiogram utilizing the precordial transitional zone, or whether it is due to abnormally shortened anterior-posterior components of both the equilateral tetrahedron and the cube systems, represents questions which cannot be answered unequivocally at this time. However, anatomical considerations would seem to place the electrical center of the heart somewhat anterior to the plane determined by the points of attachment of the extremities with the trunk. This would suggest that the correction factor for the anterior-posterior component, VB, should exceed 1.7, the value obtained mathematically when the tetrahedron is considered to be isosceles in form.[13] It then follows that a correction factor for VB of 1.2, derived for a tetrahedron of alleged equilateral configuration,[13] may be a falsely low value. Moreover, Lamb and Dimond[14] have suggested that the angle, subtended by the electrodes comprising the anterior-posterior lead of the conventional cube frame, is too small. This angle is considerably increased in their modification of the cube, despite the fact that, in most instances, the electrodes forming their anterior-posterior lead are probably in satisfactorily remote positions.

SUMMARY

1. A trigonometric method is used for the calculation of the angle between any two spatial vectors, given the angular positions of their projections on two mutually perpendicular planes. The necessary formulas and their derivations are given in the appendix.

2. A method is described for estimating the angle between the mean spatial QRS and T vectors from a 12 lead electrocardiogram. This method permits a

determination of the angular positions of the projections of the mean spatial QRS and T vectors on the transverse, as well as on the frontal plane; from these measurements the spatial angle may be calculated trigonometrically.

3. The determination of the angles between the mean QRS and T vectors from 12 lead electrocardiograms of twenty normal individuals, age 18 to 57, suggests that the upper limit of normal previously given for this determination is too low. Some of the possible reasons for this discrepancy are discussed.

4. Statistical study of the vectorcardiographic data indicates that there was a significant difference in the mean of the angles between the largest spatial and frontal QRS and T vectors obtained with the cube and tetrahedral reference frames. A significant association, as determined by regression, could not be demonstrated for either the spatial or the two planar angles obtained with these two systems. While these findings do not prove conclusively that a significant association might not exist if more cases were studied, it suggests that there would be difficulty in translating from one system to another in a given patient.

The authors are indebted to Doctor Boris Podolsky, Professor of Mathematical Physics, University of Cincinnati, for his assistance in the mathematical aspects of this study.

APPENDIX

In the Cartesian coordinate system consisting of three mutually perpendicular axes, x, y, and z, the angle, θ, formed by the intersection of two spatial vectors, V and V′, may be calculated if the angles formed by x, y, and z and the projections of V and V′ on any two of the three planes, xy, yz or zx are known. In Fig. 1, given $\propto xy$, $\propto x'y'$, $\propto yz$ and $\propto y'z'$, the derivation of the equations used in this paper for the determination of θ is as follows:

Utilizing the trigonometric formula, $\cos A = \frac{b^2 + c^2 - a^2}{2\,bc}$, where a is the side opposite, and b and c the sides adjacent to angle A, reference to Fig. 1 indicates that:

$$\cos\ \theta = \frac{V^2 + V'^2 - W^2}{2\,VV'} \tag{1}$$

$$V^2 = x^2 + y^2 + z^2 \tag{2}$$

$$V'^2 = x'^2 + y'^2 + z'^2 \tag{3}$$

$$W^2 = (x - x')^2 + (y' - y)^2 + (z' - z)^2 \tag{4}$$

$$\cos\ \theta = \frac{2xx' + 2yy' + 2zz'}{2\,VV'} \tag{5}$$

$$\frac{x}{V} = \cos\propto x;\ \frac{x'}{V'} = \cos\propto x';\ \frac{y}{V} = \cos\propto y;\ \text{etc.} \tag{6}$$

$$\cos\ \theta = \cos\propto x\ \cos\propto x' + \cos\propto y\ \cos\propto y' + \cos\propto z\ \cos\propto z' \tag{7}$$

$$\tan^2\propto x = \frac{y^2 + z^2}{x^2} = \frac{y^2}{x^2}\left(1 + \frac{z^2}{y^2}\right) \tag{8}$$

$$\tan^2\propto x = \tan^2\propto xy\ (1 + \tan^2\propto yz) \tag{9}$$

$$\cot\propto x = (\cot\propto xy)\ (\cos\propto yz) \tag{10}$$

$$\tan^2\propto y = \frac{x^2 + z^2}{y^2} = \frac{x^2}{y^2} + \frac{z^2}{y^2} \tag{11}$$

$$\tan^2\propto y = \cot^2\propto xy + \tan^2\propto yz \tag{12}$$

$$\cos\propto y = (\cos\propto yz)\ (\sin\propto x). \tag{13}$$

As in Equations (8) through (10),

$$\cot\propto z = (\tan\propto yz)\ (\sin\propto xy). \tag{14}$$

As in Equations (11) through (13)

$$\cos\propto y = (\sin\propto xy)\ (\sin\propto z) \tag{15}$$

which serves to check Equation (13).

Thus θ may be determined by utilizing Equations (10), (13) or (15) and (14) in conjunction with Equation (7).

The relationships between $\propto xy$, $\propto yz$ and $\propto zx$ may be obtained from Fig. 1 as follows:

$$\cot\propto zx = \frac{z}{x}, \tan\propto xy = \frac{y}{x}, \tan\propto yz = \frac{z}{y} \tag{16}$$

$$\cot\propto zx = (\tan\propto xy)\ (\tan\propto yz) \tag{17}$$

$$\cot\propto xy = (\tan\propto yz)\ (\tan\propto zx) \tag{18}$$

$$\cot\propto yz = (\tan\propto zx)\ (\tan\propto xy). \tag{19}$$

If desired, the values of the cosines of $\propto x$, $\propto y$, and $\propto z$ for substitution in Equation (7) may be obtained directly from the following equations:

$$\cos\propto x = \frac{\sin\propto zx}{\sqrt{(\sin^2\propto zx)\ (\tan^2\propto xy) + 1}} \tag{20}$$

$$\cos\propto y = \frac{\sin\propto xy}{\sqrt{(\sin^2\propto xy)\ (\tan^2\propto yz) + 1}} \tag{21}$$

$$\cos\propto z = \frac{\sin\propto yz}{\sqrt{(\sin^2\propto yz)\ (\tan^2\propto zx) + 1}} \tag{22}$$

The derivations of Equations (20), (21), and (22) will not be given here but may be obtained from reference to Fig. 1. Since the computations involved in their use are complex, we prefer the alternate method given above for the calculation of θ.

Before calculating the absolute value of θ, it is important to assign the proper signs to $\cos\propto x$, $\cos\propto y$, $\cos\propto z$ (and to $\cos\propto x'$, $\cos\propto y'$, and $\cos\propto z'$). The signs of these functions may be determined from the signs of x, y, and z directly, since $\cos\propto x = x/V$ etc. V is considered to be positive invariably. The signs of x, y, and z may be found from the quadrant of each of the three planes of the Cartesian coordinate system in which angles $\propto xy$, $\propto yz$, and $\propto zx$ lie. Since x, y, and z each participate in the formation of two of these three angles, the signs of x, y, and z may be determined in two different ways as a check.

REFERENCES

1. Grant, R. P., and Estes, E. H., Jr.: Spatial Vector Electrocardiography, Philadelphia, 1951, The Blakiston Company.
2. Grishman, A., Borun, E. R., and Jaffe, H. L.: Spatial Vectorcardiography: Technique for the Simultaneous Recording of the Frontal, Sagittal and Horizontal Projections. I., Am. Heart J. **41**:483, 1951.
3. Wilson, F. N., Johnston, F. D., and Kossmann, D. E.: The Substitution of a Tetrahedron for the Einthoven Triangle, Am. Heart J. **33**:594, 1947.
4. Graettinger, J. S., Packard, J. M., and Graybiel, A.: A New Method of Equating and Presenting Bipolar and Unipolar Extremity Leads of the Electrocardiogram, Am. J. Med. **11**:3, 1951.
5. Morton, D. J.: Manual of Human Cross Section Anatomy, Baltimore, 1944, The Williams & Wilkins Company.
6. Grant, R. P.: The Relationship of Unipolar Chest Leads to the Electrical Field of the Heart, Circulation **1**:878, 1950.
7. Grant, R. P.: Spatial Vector Electrocardiography, a Method for Calculating the Spatial Electrical Vectors of the Heart from Conventional Leads, Circulation **2**:676, 1950.
8. Fisher, R. A., and Yates, F.: Statistical Tables, New York, 1949, Hafner Publishing Company.
9. Fisher, R. A.: Statistical Methods for Research Workers, Edinburgh, 1950, Oliver and Boyd.
10. Duchosal, P. W., and Grosgurin, J.: The Spatial Vectorcardiogram Obtained by Use of a Trihedron and its Scalar Comparisons, Circulation **5**:237, 1952.
11. Simonson, E.: The Distribution of Cardiac Potentials Around the Chest in One Hundred and Three Normal Men, Circulation **6**:201, 1952.
12. Langner, P. H.: Geometric Model for Determining the Direction of Mean Spatial Vectors, Am. Heart J. **44**:378, 1952.
13. Cronvich, J. A., Conway, J. P., and Burch, G. E.: Standardizing Factors in Electrocardiography, Circulation **2**:111, 1950.
14. Lamb, L. E., and Dimond, E. G.: A Method for Recording Spatial Vectorcardiograms, Am. Heart J. **44**:165, 1952.

THE PROBLEM OF CALIBRATION IN HEART SOUND RECORDING

F. Lowell Dunn, M.D., and Walter E. Rahm, Jr., M.S.

Omaha, Neb.

THE importance of calibration is shown by comparing the progress of electrocardiography and of heart sound recording. Both fields began at about the same time with Einthoven and Geluk's adapation of the string galvanometer to physiologic purposes.[1] Electrocardiography progressed well in part because of (1) the small frequency spectrum involved in electrocardiographic recording, (2) the simple frequency characteristics of the first mode of the stretched string, (3) Einthoven's instrumental ability, and (4) the absence of any alternative method for recording action currents until the electron tube era of much later date. All of these combined to provide an environment in which electrocardiography became standardized. This standardization was not in conventional physical units, but instead the string galvanometer itself became the standard. An actual specification of the frequency characteristics necessary for proper electrocardiographic recording was not agreed upon until 1947. When electronic amplification became available in the twenties, its adaptation to electrocardiography was not by designing an amplifier with specified frequency characteristics, since these were known only vaguely, but instead, by trial and error, the instrument was adjusted until the records resembled those made by the string galvanometer. This traditional acceptance of the string galvanometer as the standard even included the current convention of using the 0.04 second coordinate interval and the wide line trace, the latter a necessity with the string galvanometer because of the high optical magnification of the string. The wide line can be eliminated in amplifier electrocardiographs with definite improvement in readability and accuracy of the trace. When portable electrocardiographs were introduced there was a restriction in the high frequency characteristics as compared with the best instruments used by Einthoven and Lewis but this has been only rarely criticized to our knowledge, although our studies using accurate equipment with uniform response up to several thousand cycles per second showed more accurate amplitude measurements and a definite increase in detail.[2] These unique conditions surrounding the development of electrocardiography permitted the widespread acceptance of a single instrument as a standard, and this sufficed to develop a widespread use of the electrocardiograph as an important clinical tool.

From the Cardiovascular Laboratory, Department of Internal Medicine, University of Nebraska College of Medicine, Omaha, Neb.

A portion of the funds for this study was provided by the Life Insurance Medical Research Fund, and the National Heart Institute.

Received for publication March 14, 1953.

In contrast, heart sound recording even today has neither calibration in physical units nor does it have an instrument prototype which commands any widespread acceptance. Clinically, phonocardiography is not at all widely accepted, and its usefulness is usually confined to timing a murmur or a complex rhythm. We wish to discuss some of the difficulties that have delayed the development of the heart sound recording field.

Earlier studies in phonocardiography were made with stethoscope chest pieces, rubber tubing, carbon granule microphones, and string galvanometers, or rubber diaphragm capsules fitted with small mirrors for optical deflection. To protect the microphone or the capsule from the more vigorous movements of the precordium a vent was placed in the tubing or the chest piece. This vent would, of course, critically alter the resonant characteristics of the partially enclosed air volume in a manner that was not predictable, aside from its attenuation of the low frequencies present. The combination of tubing with different lengths, vents, and diaphragms of varying rigidity and elastic qualities effectively eliminated any hope of calibration. Besides, suitable sources of sound for calibration purposes were not available until the development of vacuum tube oscillators.

In 1924, Frederick and Dodge showed clearly the futility of utilizing the stethoscope or its components as part of a scheme to produce standardized records.[3] Figure 1, reproduced from their article, shows the frequency characteristics of an open bell stethoscope, the input frequency being held at a constant amplitude level. Figure 2, also from Frederick and Dodge, shows the frequency characteristic of the amplifier and recording system with the stethoscope removed. The marked distortion produced by the stethoscope is apparent, but it should be emphasized that the vertical scale for the two figures is in transmission units, i.e., a logarithmic scale. Thus the open bell stethoscope transmits sound ten times better at 200 cycles per second than at 100 cycles per second, and at about 260 cycles it transmits several hundred times better than at 100 cycles per second. Similar curves were published by Rappaport and Sprague in 1951 and have been obtained by us.[4] These very marked variations in output and the numerous peaks in output are due to the fact that the stethoscope belongs acoustically to the group of open or closed pipes; the peaks are resonant harmonics depending upon the length, volume, and other characteristics of the tubing and chest pieces. The position of the peaks and the amplitude of transmission are affected by varying these factors. When one recalls the lack of uniformity in stethoscope design and then couples this with the variation in individual audiograms, it is not surprising that the stethoscope has become a highly personalized instrument and that stethoscopy is usually classed with the art of medicine.

Frederick and Dodge recognized the errors inherent in stethoscopic devices and stressed the importance of placing the sensitive element of the microphone in direct contact with the flesh of the patient. "The transmitter (microphone) construction provides efficient transfer of vibrational energy from the flesh or bony framework of the body to the vibratory steel element. It provides a means for coupling which serves as a mechanical transformer for body sound energy and avoids an abrupt change in the path of the waves and large attendant losses by

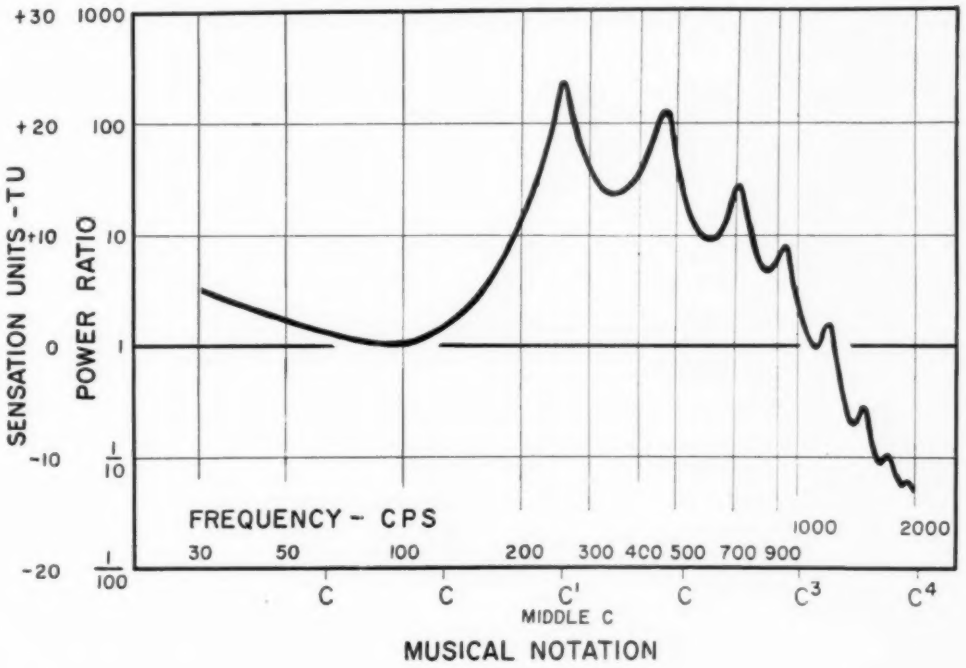

Fig. 1.—From Frederick and Dodge, Bell System Technical Journal, p. 533, October, 1924.

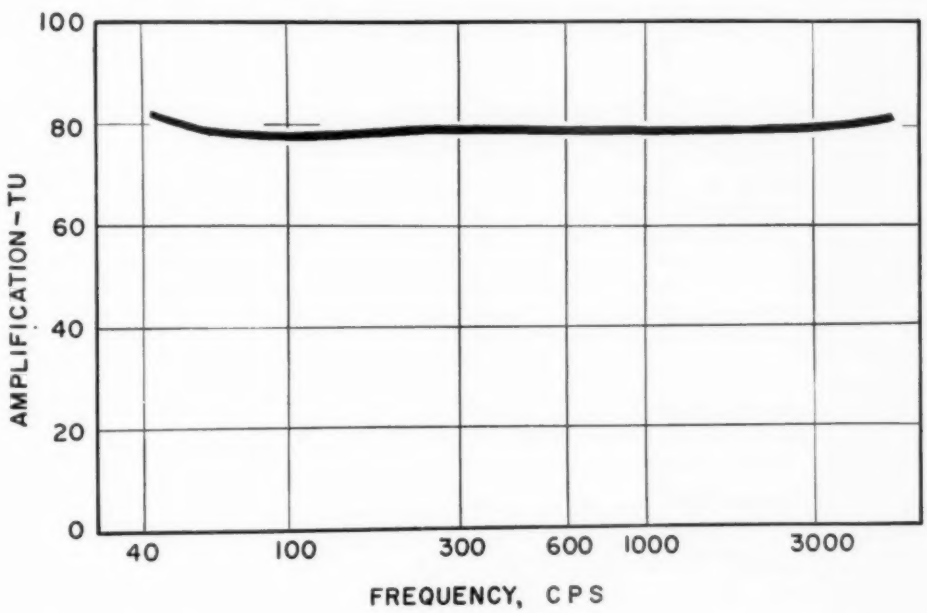

Fig. 2.—From Frederick and Dodge, Bell System Technical Journal, p. 539, October, 1924.

reflection. The system is highly damped and minimizes the distortion of the sounds of interest."[3] This seemingly basic principle was adopted in part by Mannheimer and some others but is not used at all universally in heart sound recording.[5] Rappaport and Sprague have in general used various chest pieces so that the precordial vibrations were conducted to the sensitive element of the microphone through air chambers of various capacities and shapes. In some cases these chest pieces were for the purpose of providing acoustic resonance of certain desired weak sounds. Such chest pieces, when the volume is sufficiently small so that resonance does not occur at the frequencies being studied, act as simple attenuators, but when utilized for resonant amplification they introduce the same complexity in response illustrated in Fig. 1. Hence, their use interferes with the problem of standardization in physical units, and standardization occurs only when a specific design is widely adopted. At the present time, amplifier design eliminates the need to resort to acoustic resonators since ample amplification can be obtained by electronic means. Johnston and Overy[6] used air transmission in their method but at the low frequencies studied acoustic resonance would not be involved. They did not describe their calibration technique which should include the variation in response with frequency.

The frequency range necessary for heart sound recording has not been determined completely. Our studies in 700 cases using equipment which separated the vibrations into three frequency zones are in accord with Frederick and Dodge's early observations using selective filters. These studies indicated that the upper limit was in the region of 1,000 cycles per second.[3] This is a much higher frequency than most string galvanometers and oscillographs will respond to, accurately. Williams[7] made a careful study of the design problems in string galvanometers, and instruments with frequency responses up into the range of thousands of cycles per second were made but never had any widespread usage because of cost and the development of electronic amplification. Both string galvanometers and oscillographs, being stretched-wire or tension types of instruments, have frequency curves which are uniform over only limited ranges. These ranges vary markedly with design. Curves of this class of instruments were illustrated in a previous discussion by us on electrocardiography.[2] This class of recorders has been used widely in phonocardiography and introduces a further complication in standardization because of frequency limitations and resonance phenomena. These difficulties are eliminated by the use of cathode ray recording systems.

An important part of the difficulty in standardization of visual heart sound records is confusion as to objectives. Frederick and Dodge constructed an instrument to accurately record vibrations (Fig. 2) and then knowingly added the distortion necessary to make the result similar to the stethoscope (Fig. 1). There is a widespread impression that a heart sound when recorded for visual observation should be a visual pattern of what is heard. Superficially this does not seem unreasonable but the concept will not stand analysis if the objective is to provide a record that is standardized or widely acceptable. Some of the difficulties are as follows: (1) There are marked variations in even the normal

range of hearing. The so-called normal audiogram is a smoothed curve of thousands of hearing tests. Individual audiograms differ markedly, even as high as 20 decibels. As Fletcher states, "It is thus seen that each person has a hearing acuity which is peculiar to himself."[8] These marked variations in individual acuity make the smoothed audiogram a poor reference standard. (2) The clinician often accepts his stethoscope as being a norm but there is no such thing as a standard stethoscope. In addition to the difficulties discussed with reference to Fig. 1 the tightness of the fit of the earpieces affects the attenuation, particularly the low frequencies. The diaphragm types of stethoscopes introduce added variables depending upon the size, thickness, elasticity, and damping due to the nature of the diaphragm and the manner in which it is applied to the chest. (3) Wever and his associates' studies on distortions of hearing at low frequencies should be stressed. They showed that when the ear drum is subjected to low frequency oscillations in the form of a sine wave of high purity that distortion occurs in hearing tests in the human and in the cochlea nerve potentials of the guinea pig. These distortions were interpreted as clicks and noises, descriptions akin to split first sounds, impure first sounds, and short murmurs. Although the distortion increases with intensity it is present for low tones even at moderate levels of stimulation.[9] A recent stethoscopic amplifier that is commercially available was considered superior because of the increased number of split first sounds that could be heard. Our visual records made with accurate equipment show the lower frequency components characteristic of the normal first heart sound and provide support for stating that a significant portion of the characteristics that make up the first heart sound as heard with the stethoscope may be due to aural distortion. This concept has been of value in the loudspeaker demonstration of heart sounds for classroom use since it implies the importance of large cone speakers with good low frequency output, the careful selection of low frequencies in the filtering system, and the arrangement of speaker and students in such a manner that the zone of acoustic radiation is properly placed. Excess low frequency, however, produces a booming component. Other arguments could be presented, but they add up to the point that standardization designed around the stethoscope or an aural standard involves too many arbitrary assumptions to be practical.

If we look at heart sound recording as a problem in vibration recording, there are two immediate advantages: (1) we are making a direct measure of mechanical forces, i.e., the direct result of cardiodynamics of which sound is a derivative, and (2) standardization can be obtained in physical units, i.e., force, length, time. Elsewhere we have discussed the practical design of the pistonphone and its application to microphone calibration.[10] This provides an independent and absolute source for calibration. The operation of the pistonphone is time consuming and requires considerable skill but rapid and highly stable secondary calibrators can be constructed using a telephone receiver as a source of vibration, the diaphragm substituting for the oscillating piston. These are calibrated by substitution. If use is made of an audio oscillator to drive the receiver and a milliameter adjusted with a proper series resistor, the meter can be made to read directly in dynes per square centimeter. The stability of such an

assembly is of the same order as that of the meter so that this combination provides a method for (1) studying the accuracy of heart vibration and sound recording equipment, and (2) setting heart sound equipment to any desired and reproducible sensitivity.[11]

With the calibrating equipment summarized we have studied seven crystal microphones over a period of two years and determined (1) frequency response, (2) uniformity in operation, (3) changes in sensitivity and capacity, (4) variations with temperature, and (5) effects of aging.[11] Since the curve shapes were essentially identical below 1,000 cycles per second for the seven microphones, Fig. 3 illustrates the curve of one microphone. Above 1,000 cycles the curves vary somewhat and in the region of 1,500 cycles and above there is a series of maxima associated with details of design and mounting. These curves agree with analagous data furnished by the manufacturer but differ from Mannheimer's graph in the 300 cycle range, the deviation being interpreted by us as associated with resonance phenomena in the pistonphone assembly. It deviates widely from the notation on frequency response for this type of microphone by Frost.[12,13]

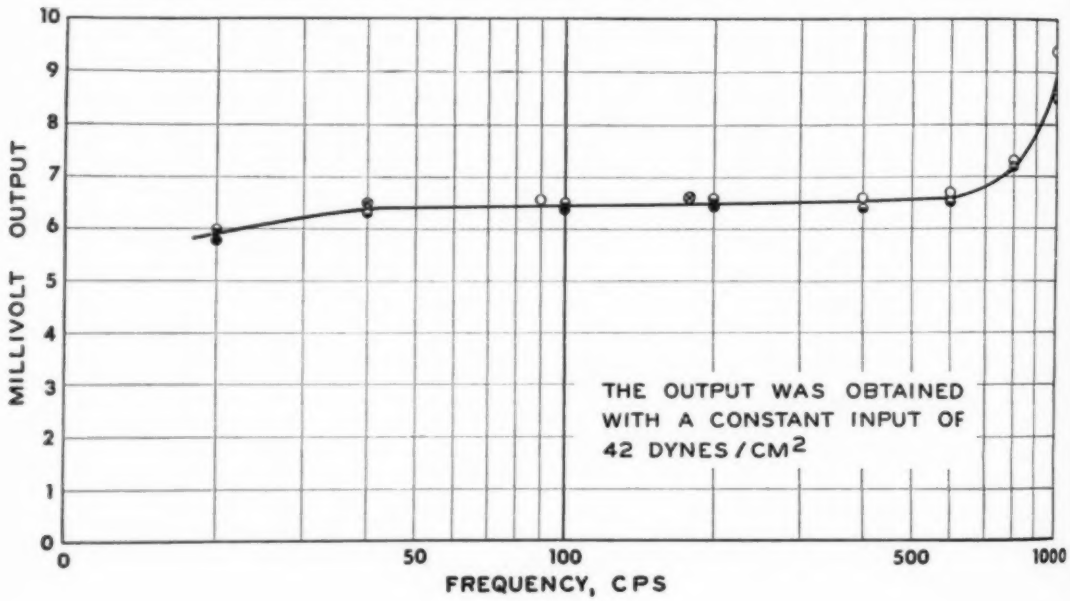

Fig. 3.

Since the present calibration technique has been available we have been using three microphones simultaneously for studying different areas of the precordium.[14] The microphones, having the same shape of frequency curves, needed to be standardized at only a single frequency, usually 100 cycles per second. This can be done in less than a minute per microphone, and the net result is a record reading in so many dynes per centimeter deflection on the finished record. This converts phonocardiography from being an adjunct to the stethoscope into the field of vibration studies and makes a practical tool for the study of cardiodynamics. A vibrational approach was implied in several reports by Smith and associates but was not further developed.[15]

The idea of "Total Vibrations," as suggested by Kountze, being recorded on a single tracing is somewhat misleading. The combination of a crystal microphone such as the type we have studied, a resistance-capacity amplifier with a uniform response to frequencies from 10 to 1,000 cycles per second, and a cathode ray tube for recording can be made to respond uniformly to all vibrations over a wide range of frequencies but this will not suffice for heart sound recording. The slower vibrations of the heart have a large thrust as compared with the much finer movements at higher frequencies. If the amplifier is adjusted to give a desirable amplitude trace of the lower frequencies, then the higher frequencies will not be of sufficient amplitude to be visible on the trace. If the amplifier is adjusted to show the higher frequency components, then the low frequency components will block the amplifier or result in overshooting. For the study of a particular portion of the frequency spectrum electric filters are necessary. A discussion of electric filters is too technical to include here, but several points should be stressed. There are two broad classes of electric filters, (1) those made up with combinations of inductance and capacity, and (2) those utilizing combinations of resistance and capacity. The first class is widely used in the communications industry where by proper design they can be made to respond to a very narrow band of frequencies, i.e., be highly selective. Fundamentally, they are resonating circuits and are designed to have a selected frequency response range. If not critically damped, they have the defect of "ringing" and any sufficiently strong signal will start them oscillating. The period of oscillation is not necessarily the frequency of the incoming signal but the natural period of the filter. This is the same problem of resonance discussed earlier in connection with stethoscope attachments, string galvanometers, and oscillographs, and a study of many published phonocardiograms shows that resonance and ringing have not been avoided. The critical damping of these circuits minimizes this resonance effect but with some loss of selectivity or sharpness. Such filter circuits are well adapted to isolate narrow bands for the study of steady state vibrations, but the time required for build-up and decay, even when critically damped, makes them poor systems for studying transients such as occur in the heart cycle. In contrast, the second class of filters has no natural period, and hence ringing and resonance are no problem. The character of the heart vibrations being aperiodic in occurrence is well suited to the use of this type of filter since the lower frequencies of the heart sound have high energy value, and the energy content becomes less as the frequency is increased. Hence, the problem is the simple one of designing high pass filters to cut off varying portions of the lower frequencies. Since no filter has an abrupt cutoff any careful analysis of the intensity at a specified frequency requires a knowledge of the output curve of the recording system used. At the present time to record adequately the range of frequencies present down to about 10 cycles per second requires three frequency bands. Fewer bands than this can result in a failure to record sounds of known clinical importance, e.g., interauricular septal leaks or the diastolic murmur of mitral stenosis.

REFERENCES

1. Einthoven, W., and Geluk, M. A. J.: Die Registierung der Herzton, Arch. f. d. ges. Physiol. **57**:617, 1894.
2. Dunn, F. Lowell, and Rahm, Walter E., Jr.: Electrocardiography: Modern Trends in Instrumentation and Visual and Direct Recording Electrocardiography, Ann. Int. Med. **32**:611, 1950.
3. Frederick, H. A., and Dodge, H. F.: The Stethophone, An Electrical Stethoscope, Bell System Technical Journal **3**:531, 1924.
4. Rappaport, M. D., and Sprague, H. B.: The Effects of Tubing Bore on Stethoscope Efficiency, AM. HEART J. **42**:605, 1951.
5. Mannheimer, E.: Calibrated Phonocardiography and Electrocardiography, Acta paediat. (supp. 2) **28**:1, 1940.
6. Johnston, D. J., and Overy, D. C.: Vibrations of Low Frequency Over the Precordium, Circulation **3**:579, 1951.
7. Williams, H. B.: The Einthoven String Galvanometer, a Theoretical and Experimental Study, Part I. Rev. Sci. Inst. **9**:129, 1924. Part II, J. Opt. Soc. America and Rev. Sci. Inst. **13**:313, 1926.
8. Fletcher, H.: Speech and Hearing, New York City, 1943, D. Van Nostrand Co., pp. 140-2.
9. Wever, E. G.: Theory of Hearing, New York City, 1949, John Wiley and Son, chapter 13.
10. Dunn, F. Lowell, and Rahm, Walter E., Jr.: Microphone Calibration at Low Frequencies in Absolute Units, Arch. Otolaryng. (In press.)
11. Dunn, F. Lowell, and Rahm, Walter E., Jr.: Electrostethography. III. Crystal Microphone Characteristics at Low Frequencies, AM. HEART J. **45**:519, 1953.
12. Shure Bros., Inc., Chicago, Ill. Personal communication from B. B. Bauer.
13. Frost, Jorgen: Phonocardiographic Studies on Gallop Rhythm, Acta Med. Scandinav. **123**:268, 1949.
14. Dunn, F. Lowell, and Rahm, Walter E., Jr.: Electrostethography II. New Method for Study of Precordial Transmission of Cardiodynamics, AM. HEART J. **44**:95, 1952.
15. Smith, J. R., Edwards, J. C., and Kountz, W. B.: The Use of the Cathode Ray for Recording Heart Sounds and Vibrations. III. Total Cardiac Vibrations in One Hundred Normal Subjects, AM. HEART J. **21**:288, 1941.

BERIBERI HEART DISEASE

AARON BURLAMAQUI BENCHIMOL, M.D., AND PAUL SCHLESINGER, M.D.

RIO DE JANEIRO, BRAZIL

THE clinical syndrome of beriberi heart disease has been well established since the classical descriptions of Aalsmeer and Wenckebach[1a], Keefer[2] and Shimazono[3] in the Orient, and the reports of Weiss and Wilkins[4] among others who studied the cardiovascular manifestations of this disease in the western hemisphere.

Notwithstanding the fact that the occurrence of cardiac beriberi now is well recognized in several countries, it still is described among the rare types of heart disease in most of the modern textbooks of cardiology.[5-8] However, in view of our experience in this country, we have reason to believe that it is not such an unusual condition and that the apparent infrequency of beriberi heart disease is due to the fact that many cases are not recognized as such and are often confused with other more common and well-known types of heart disease.

During a three-year period, since our attention was directed to this problem we have identified a series of twenty-two patients with beriberi heart disease, including occasional instances in which other associated etiologic factors were encountered.

As a result of the well-documented observations reported by Weiss and Wilkins[4] in the United States, it was pointed out that the clinical picture of cardiac beriberi in this hemisphere frequently differed considerably from the classical syndrome originally described in the Orient. Thus, right-sided heart failure was not a common occurrence as an isolated finding but was associated usually with signs and symptoms of left ventricular insufficiency such as dyspnea, orthopnea, and cardiac asthma. Furthermore, the frequent absence of the hyperkinetic circulatory syndrome, which is considered so highly characteristic of beriberi heart disease in the Orient, deprives the physician of one of the important diagnostic features of this condition. Under these circumstances it is not surprising that such cases are often misleading, since they so closely resemble other more common types of degenerative heart disease. These findings led to the establishment of less rigid criteria for the diagnosis of beriberi heart disease[11] in which the role of chronic alcoholism was particularly emphasized as the main cause of the vitamin deficiency.[4] In the last two decades a number of reports have appeared in the literature, as a result of which most clinicians have become

From the Hospital dos Servidores do Estado, and the Fifth Medical Clinic (Service of Professor Luiz Capriglione) of the National Faculty of Medicine, University of Brazil, Department of Cardiology, Hospital Moncorvo Filho, Rio de Janeiro, Brazil.

Received for publication March 19, 1953.

well aware of the cardiovascular manifestations of beriberi notwithstanding the considerable lack of uniformity of the clinical syndrome. The importance of beriberi heart disease in Brazil was recognized since the early papers of Silva Lima[9] and others,[10,19] published almost one hundred years ago, and confirmed by a number of recent reports on this subject.[13-16]

Our observations include twenty-two cases which have been followed for periods varying from a few weeks to almost three years. It is our purpose in this paper to present the pertinent findings in these patients and to describe the clinical syndrome of beriberi heart disease as we have observed it to occur in this country.

Etiology.—Whereas thiamin deficiency among the oriental populations is due usually to an inadequate diet, most cases of beriberi heart disease in this hemisphere occur as a result of chronic alcoholism. All our patients were heavy drinkers, and only 50 per cent had a history of an associated dietary deficiency. However, there was no evidence of malnutrition in any instance, because of the high caloric content of the alcoholic beverages which were consumed. Since the incidence of chronic alcoholism is far greater than that of beriberi heart disease, it is evident that other associated factors such as physical exertion, infectious diseases, thyrotoxicosis, pregnancy and so forth must also play a role. At any rate the so-called alcoholic myocarditis, which was formerly believed to be due to the direct effects of alcohol on the heart, is not accepted by the most recent investigators. The excessive intake of alcohol predisposes to beriberi by inducing thiamin deficiency which is the primary factor in this condition. That alcohol does not play a direct role in this disease has been proved by the complete reversal of the clinical picture following the administration of large doses of thiamine to patients who maintain their usual intake of alcohol.[4c] Furthermore, many cases have been observed in which the development of cardiac failure occurs for the first time, following a period of several weeks or even months of total abstinence from alcohol.[4b] This is usually seen in individuals with digestive disturbances which undoubtedly maintain the thiamine deficiency. In two of our patients (Cases 2 and 19) we were able to note that the onset of heart failure occurred one and two years, respectively, after they had refrained almost completely from the use of alcoholic beverages which were previously consumed in large quantities. All our patients were apparently well nourished because of the high caloric intake provided largely by alcohol; this presumably compensated for the poor dietary regimen in a considerable number of cases. Since the thiamine requirements of the human body are dependent upon the total caloric intake and the carbohydrate content of the diet, an increase in the latter predisposes to beriberi by increasing the metabolic demands for vitamin B_1.[17] This has been proved by the consistently unsuccessful attempts to induce experimental thiamine deficiency in pigeons deprived of this vitamin and fed on diets consisting predominantly of fats rather than carbohydrates.[18] Although the excessive intake of alcohol increases the body requirements for thiamine, the caloric content of the diet is maintained at a high level. This affords an explanation for the diminished appetite of these patients, aggravated by the associated gastrointestinal disturbances which in turn decrease the absorption of thiamine. In addition,

the frequent involvement of the liver in these patients causes a further disturbance in the storage and utilization of vitamin B_1. It is well known that this vitamin represented by thiamine pyrophosphate or diphosphothiamine is an ester of pyrophosphoric acid, functioning as a coenzyme (cocarboxylase) in carbohydrate metabolism. Thus, vitamin B_1 leads to the disintegration of pyruvic acid which is derived from lactic acid. The decarboxylation of pyruvic acid is catalyzed by specific protein enzymes in the presence of this cofactor designated as diphosphothiamine. This "prosthetic group" (protein enzyme and cocarboxylase) acts upon the pyruvic acid which undergoes oxidation or utilization in other metabolic processes. Lactic acid is continuously transformed or disintegrated, while an excess of pyruvate inhibits the dehydrogenation of this substance. In thiamine deficiency, pyruvic acid accumulates in the tissues and can be used as a clinical test for thiamine deficiency. It has been claimed, however, that the increase in blood pyruvic acid levels is not a specific finding in this type of vitamin deficiency. Several tests of greater diagnostic value have been recently proposed and are based upon the determination of the blood levels of pyruvic and lactic acids after the administration of glucose, followed or not by exercise.

Sex.—All our patients were men, notwithstanding the fact that patients of both sexes were admitted to the medical services in which these observations were carried out. This is probably explained by the fact that chronic alcoholism is comparatively rare among women in Brazil.

Age.—The great majority of our patients belonged to the younger age groups, largely between 30 and 40 years of age, with a single exception (Case 12) of a 52-year-old patient in whom pathologic examination ruled out the possibility of coronary sclerosis.

Occupation.—All but six of our cases were engaged in employments associated with great physical exertion. Thus, the thiamine requirements were increased, thereby precipitating the development of beriberi heart disease.

Clinical Features.—Since the signs and symptoms of cardiac beriberi vary considerably with the severity of the disease and the type of cardiovascular dysfunction, we shall attempt to outline our general impression of the clinical picture according to the series of cases which we have observed personally.

Dependent edema was the most striking feature and was present as an initial sign in all but two patients (Cases 12 and 21). In fourteen cases edema of the lower extremities occurred for several weeks as the only manifestation of the disease, whereas dyspnea appeared simultaneously in six instances. Paroxysmal dyspnea followed by orthopnea occurred as an isolated initial symptom in two cases. However, the majority of our patients complained of varying degrees of dyspnea either in the early stages associated with other symptoms, or later in the course of the disease.

Clinical or roentgenological signs of pulmonary congestion were observed in nineteen cases. It is evident, therefore, that signs of left ventricular failure were present in most of our patients. This observation seems to confirm the opinion of Weiss and Wilkins,[4b,4c] concerning the occidental form of beriberi heart disease, in which isolated right ventricular insufficiency was an unusual

finding. Only five patients in this series had ascites which attained considerable proportions in Case 8. Pleural effusion was an equally rare finding and occurred as a right hydrothorax (Fig. 1) in three patients. The above mentioned manifestations, in addition to hepatomegaly which was found in all our cases, were largely attributed to the presence of congestive heart failure. Since hypoproteinemia has been considered as one of the possible causes of edema, the serum protein levels were obtained in thirteen instances and were found to be lower than 6 Gm. per cent in six cases. However, no correlation could be established between these findings and the degree of clinical edema. Although hypoproteinemia has been reported as a common occurrence in beriberi[11b,12] it probably does not play a major role as a cause of edema, since the latter frequently disappears entirely without a corresponding change in the serum protein concentrations. A residual hepatomegaly remained in four of our patients following full

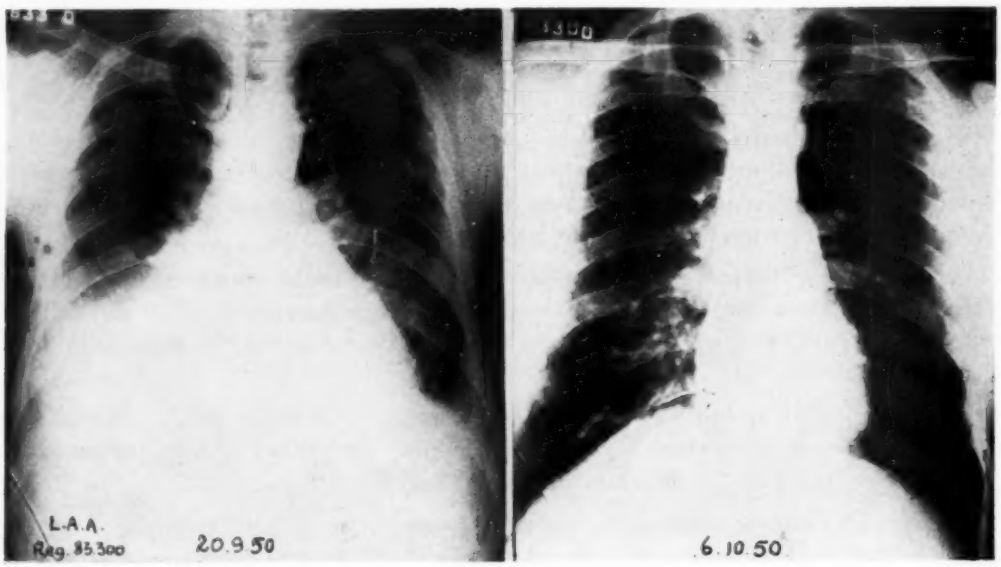

Fig. 1 (Case 22).—(L.A.A.)—The initial roentgenogram shows an increased heart shadow with signs of pulmonary congestion and a right-sided pleural effusion. Two weeks later, after thiamine treatment, there is a marked decrease in heart size and disappearance of the pre-existent right hydrothorax.

recovery from congestive heart failure. This finding was interpreted as due to an incipient cirrhosis of the liver and was still evident one year later in Cases 6 and 16 who were otherwise in excellent physical condition. Only three of our patients complained of palpitations, which was quite a low incidence as compared to other reports in the literature. Cyanosis was equally uncommon and of a mild degree, occurring in less than one-third of our series.

Cardiac auscultation revealed soft apical systolic murmurs (Grades 1 or 2) in the majority of our cases and were interpreted as evidence of functional mitral insufficiency, since they decreased considerably or disappeared entirely, following cardiac compensation. Diastolic murmurs of a slight degree were heard in four patients, one of whom (Case 17) had an associated congenital deformity of the

pulmonary valve. Although the possibility of aortic insufficiency was suggested in these cases, it was completely ruled out by the autopsy findings in one instance and by the disappearance of the diastolic murmur in the others, following clinical improvement. Another common finding was a transient gallop rhythm during the period of heart failure. The majority of our patients had an accentuated pulmonary second sound which was reduplicated in six instances. Tachycardia was present almost always, the heart rate being over 90 in all but six patients. A typical water-hammer pulse occurred in only three cases of our series. A transient bradycardia, associated with other signs of vagal activity such as hypersensitive carotid sinus reflex, was present occasionally during convalescence.

The *blood pressure* variations in cardiac beriberi have been previously emphasized[2] and cases have been reported with normal, elevated, or low blood pressures. An increased pulse pressure is a common finding, particularly in the advanced forms of the disease (five patients in this series) and seems to be due to a diminished vascular tonus leading to peripheral vasodilatation. Diastolic pressures of zero have been reported as frequent occurrences in oriental beriberi heart disease.[1,3] In one of our patients (Case 16) whose initial blood pressure was 170/70 mm. Hg we were able to observe the development of a mild diastolic hypertension: 160/110 mm. Hg (Fig. 2), following cardiac compensation. This case was discharged with the presumptive diagnosis of beriberi heart disease associated with essential hypertension. This initial impression, however, was not confirmed since a subsequent revision revealed a blood pressure of 136/96 mm. Hg with complete normalization of both radiologic (Fig. 3) and electrocardiographic changes. A transient hypertension during congestive heart failure was not an infrequent finding in our cases of beriberi heart disease, some of which remained at hypertensive levels for several weeks after the subsidence of all other cardiovascular manifestations. Ten of our twenty-two patients showed signs of rapid circulation as judged by the circulation times; however, only five of these had typical hyperkinetic syndromes with an increased pulse pressure, a bounding pulse, a normal circulation time in the presence of congestive failure and increased cardiovascular pulsations on fluoroscopic examination. Venous pressure determinations performed in eighteen cases were found to be markedly elevated in all instances with the exception of Case 10 who had a venous pressure of 13 cm. on admission which later decreased to 8 cm. following cardiac compensation. Arm-to-tongue circulation times were carried out in all of our cases. Values above 15 seconds were found in eleven patients, four of which showed markedly prolonged circulation times, whereas in the remaining seven it was below 20 seconds. In the other eleven patients which comprised 50 per cent of our series, circulation times were found to be well within normal limits during the stage of congestive heart failure. Since this has been considered a classical finding in beriberi heart disease as reported by others[1,4,21] it is interesting to note that it was absent in one-half of our cases.

Polyneuritis was a most frequent finding, since it was observed in twenty patients. In five of these, the neuritic manifestations were of a mild degree, whereas in fourteen cases they were quite evident. No cases were observed of the more severe forms of polyneuritis. Three cases showed signs of *pellagra* with associated glossitis and cheylitis in one instance. There were three cases of

anemia, of which two were mild forms, whereas the third (Case 10) showed a more severe degree of this condition.

The clinical manifestations which we have just described are usually sufficient to suggest the diagnosis of beriberi heart disease, particularly if the patient happens to be a chronic alcoholic. It is evident, however, that the roentgenologic and electrocardiographic changes, as well as the therapeutic effects of thiamine, are far more significant diagnostic features of this type of heart disease.

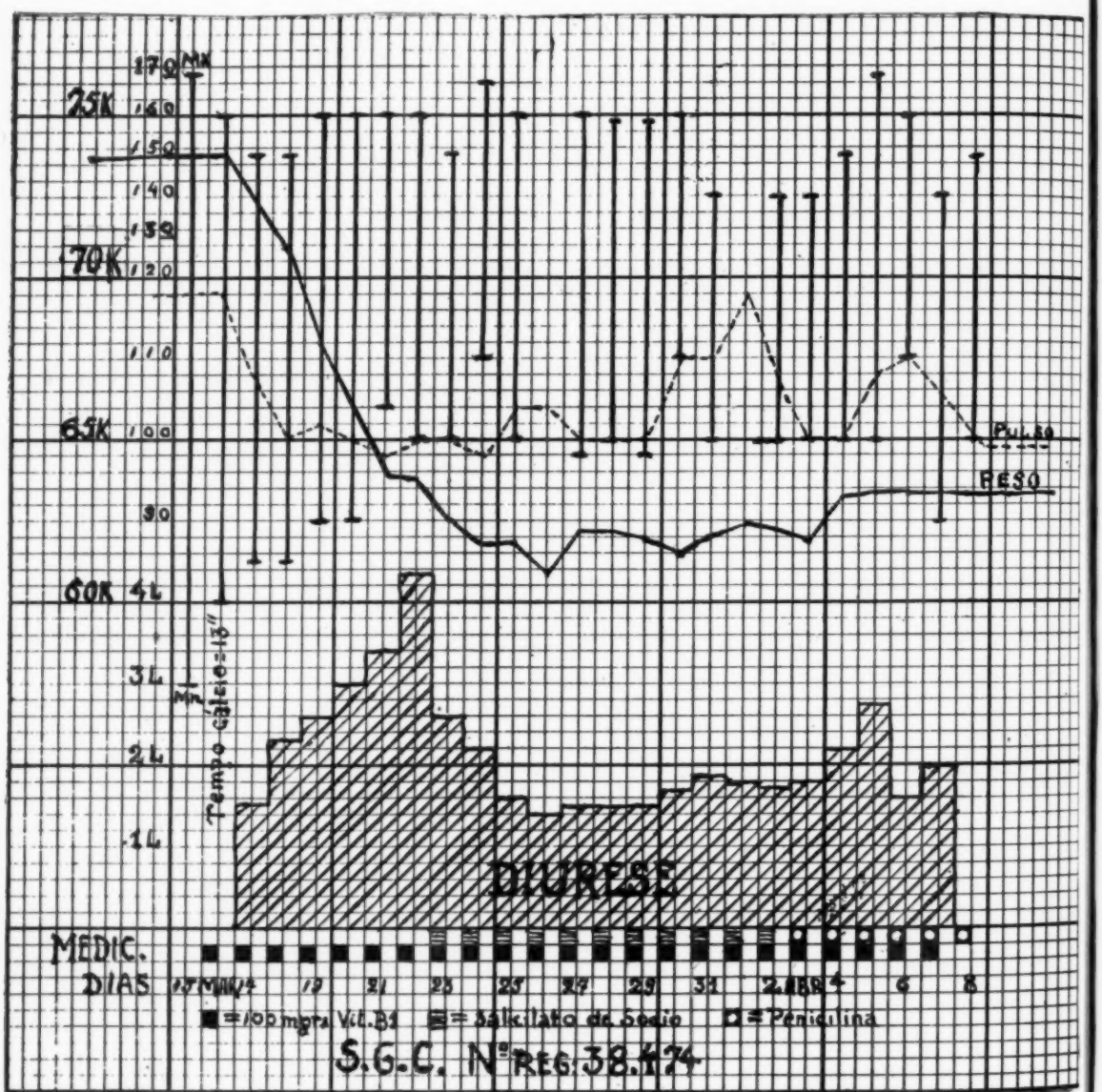

Fig. 2 (Case 16).—(S.G.C.)—Diagrammatic representation of the clinical course of a patient with cardiac beriberi, showing the initially wide pulse pressure which subsequently decreased following marked diuresis and weight loss, as a result of bed rest and parenteral administration of vitamin B_1.

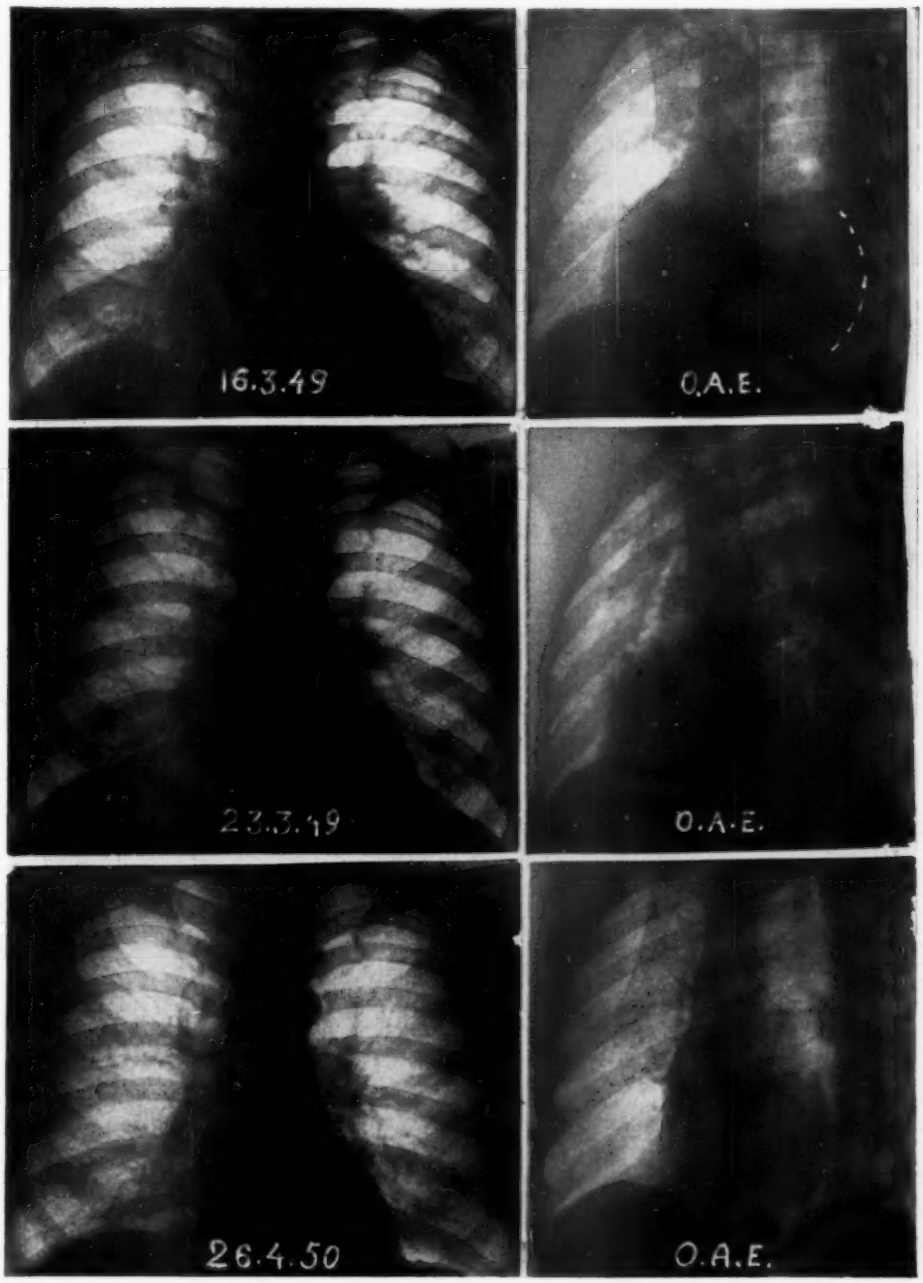

Fig. 3.—Same case as Fig. 2. (S.G.C.), showing complete normalization of a markedly enlarged heart. A definite decrease in the cardiac area occurred initially after one week of thiamine treatment and became more evident in the course of prolonged medication.

The *roentgenologic findings* in cardiac beriberi are not typical, although a reduction in heart size following a favorable response to thiamine treatment is included among the important features of this condition. In the Orient it has been repeatedly emphasized that cardiac enlargement was due largely to dilatation of the right chambers[1,20,22] with a prominent pulmonary conus which simulated either mitral stenosis or an aneurysmal dilatation of the pulmonary artery.[1] In the Occident, however, these roentgenologic features were not observed usually, since left ventricular enlargement as well as signs of pulmonary congestion were equally present in most instances.[4,12,23,25] Most of our patients exhibited cardiac enlargement with or without roentgenologic signs of pulmonary congestion. Nine patients (Cases 1-3, 6, 7, 14, 16, 19, 22) were discharged with normal heart size. Five of these cases showed marked cardiac enlargement on admission, whereas the remaining four were only slightly above normal limits. Figures 1, 3, 4, and 5 illustrate typical examples of a reduction in heart size following thia-

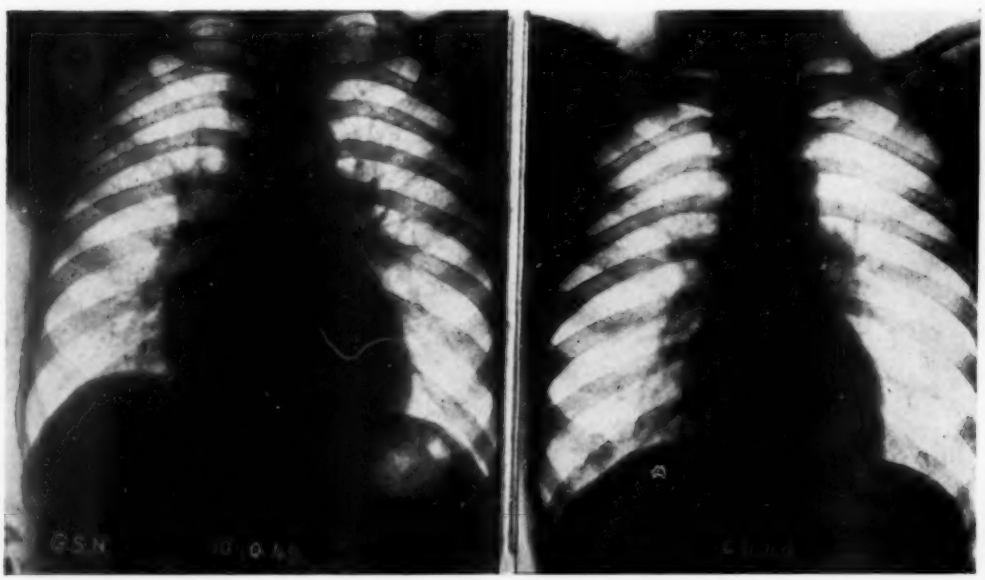

Fig. 4 (Case 1).—(G.S.N)—Roentgenologic signs of predominant right chamber enlargement in addition to hilar congestion, preceding vitamin administration. Notwithstanding the fact that the patient did not submit to bed rest or salt restriction, there was a marked decrease in heart size after three weeks of thiamine treatment.

mine medication. With the exception of Fig. 5, roentgenologic signs of pulmonary congestion and increased hilar shadows can be observed clearly in addition to a right hydrothorax in Case 22 (Fig. 1). Figure 4 is our only case of predominant enlargement of the right cardiac chambers, and Fig. 5 is another isolated example in our series of a prominent pulmonary conus which disappeared following clinical improvement. It should be noted, however, that cardiac enlargement is not always completely reversible and even those who consider the roentgenologic reduction in heart size as one of the main diagnostic features of beriberi heart disease[45] observe that this may fail to occur in the advanced stages of thiamine

deficiency. Thus, cardiac dilatation may be only partially reversible or completely irreversible according to the degree and the duration of myocardial involvement. Such cases are due to long-standing interstitial edema and hydropic degeneration which eventually lead to myocardial fibrosis. These instances of chronic cardiac beriberi often simulate other types of heart disease such as coronary sclerosis.[27] In five of our patients (Cases 5, 8, 10, 13, and 15) with predominant left ventricular enlargement there was only a partial reduction in

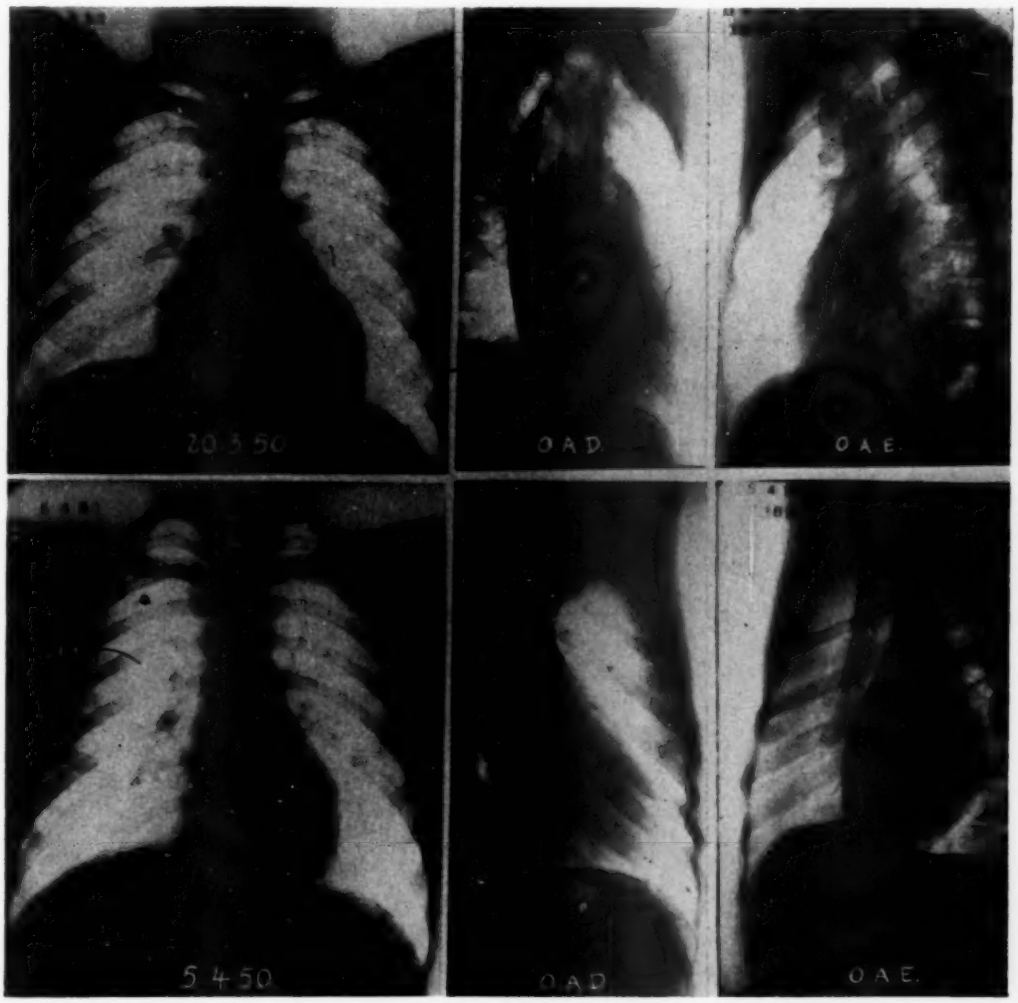

Fig. 5 (Case 19).—(S.O.R.)—Moderate cardiac enlargement with a prominent pulmonary conus in the right anterior oblique position, in addition to left ventricular hypertrophy. The lung fields are clear. After two weeks of thiamine treatment the heart size is normal with complete disappearance of the prominent pulmonary conus.

heart size after thiamine medication. Fluoroscopic studies were carried out in seven cases, three of which exhibited typical signs of a hyperkinetic cardiovascular syndrome as shown by the ample pulsations of the cardiac contour.

The *electrocardiogram* frequently reveals definite abnormalities indicating myocardial damage. Although these changes are nonspecific, their disappearance following thiamine treatment constitutes an important diagnostic and prognostic feature of cardiac beriberi. In the initial publications[1,2,20] the electrocardiographic changes were mentioned as being either slight or nonexistent. Subsequently, however, it has been shown repeatedly that these graphic abnormalities are encountered frequently in cases of beriberi consisting mainly in changes of the T wave, of the QRS complexes and of the Q-T interval.[4,12,13,21,26,29-33] Experimental studies on thiamine deficient rats[34,35] and dogs[36] revealed electrocardiographic changes which resembled closely those recorded in human observations. Electrocardiograms were obtained in all our patients, including serial tracings in eighteen patients. Regular sinus rhythm occurred in all but one case (21) in which the presence of ventricular premature beats was attributed to digitalis. The absence of significant arrhythmias has been previously emphasized in this condition,[1,11,37] although Weiss and Wilkins[4] mention auricular and ventricular premature beats in a small percentage of their cases. Normal tracings were recorded in two patients of our series (Cases 7 and 14) one of which had only a single electrocardiogram limited to the standard leads.

Most authors[2,4,12,21,26,28,30-33,38] have called attention to the occurrence of reversible T-wave changes, such as flattening or inversion of this deflection, as the main electrocardiographic abnormalities in beriberi heart disease. Low voltage of the T waves was observed in five of our patients (Cases 1, 4, 9, 10, and 17) either as an isolated abnormality or associated with a decrease in the amplitude of the QRS complexes illustrated in Fig. 6. In this case a definite increase in voltage was apparent after three weeks of thiamine medication. One year later, however, the T waves were peaked and showed a further increase in amplitude which was not an uncommon finding in most cases with a favorable clinical outcome. It is important to recognize that some cases of beriberi heart disease do not show a complete normalization of the electrocardiogram after appropriate therapy, and that this should not necessarily rule out the diagnosis of vitamin B_1 deficiency. In Case 9, for instance, (Fig. 7), the QRS and T-wave abnormalities remained unchanged after eight days of intensive thiamine medication. This patient died on the eleventh day of admission in advanced congestive heart failure and had necropsy confirmation of the clinical diagnosis of cardiac beriberi. The occurrence of T-wave inversion of variable degrees has been observed by a number of investigators in this type of heart disease.[11,12,26,28,38,39,40] Some authors[38] reported this finding only in far advanced cases. Inverted T waves were recorded in three patients of our series (Cases 3, 8, and 13). In Case 3 (Fig. 8) there was a slight T-wave inversion in Lead aV_L which became progressively less marked in serial tracings with subsequent normalization. This patient had a mild form of cardiac beriberi, notwithstanding the previously mentioned observations[38] that T-wave inversion occurs predominantly in severe cases of thiamine deficiency. The remaining two patients showed acutely inverted T waves, suggesting myocardial ischemia. In spite of the severe circulatory condition in both cases, the T waves reverted to a normal configuration following clinical recovery. In Case 8 (Fig. 9) the T waves became progressively more inverted during the stage of clinical improvement, a fact which has been previously emphasized by several authors.[4,12,28,30]

Electrocardiographic signs of left ventricular hypertrophy occurred in eight patients, four of whom showed associated T-wave changes. In Cases 3, 8, and 13 the T-wave abnormalities were thought to be of the primary type since there was complete normalization after the administration of vitamin B_1. It is interesting to note that the tall R waves remained unchanged or decreased very slightly (Case 8) indicating a persistent left ventricular enlargement. These observations suggest that cardiac dilatation may be undistinguishable from

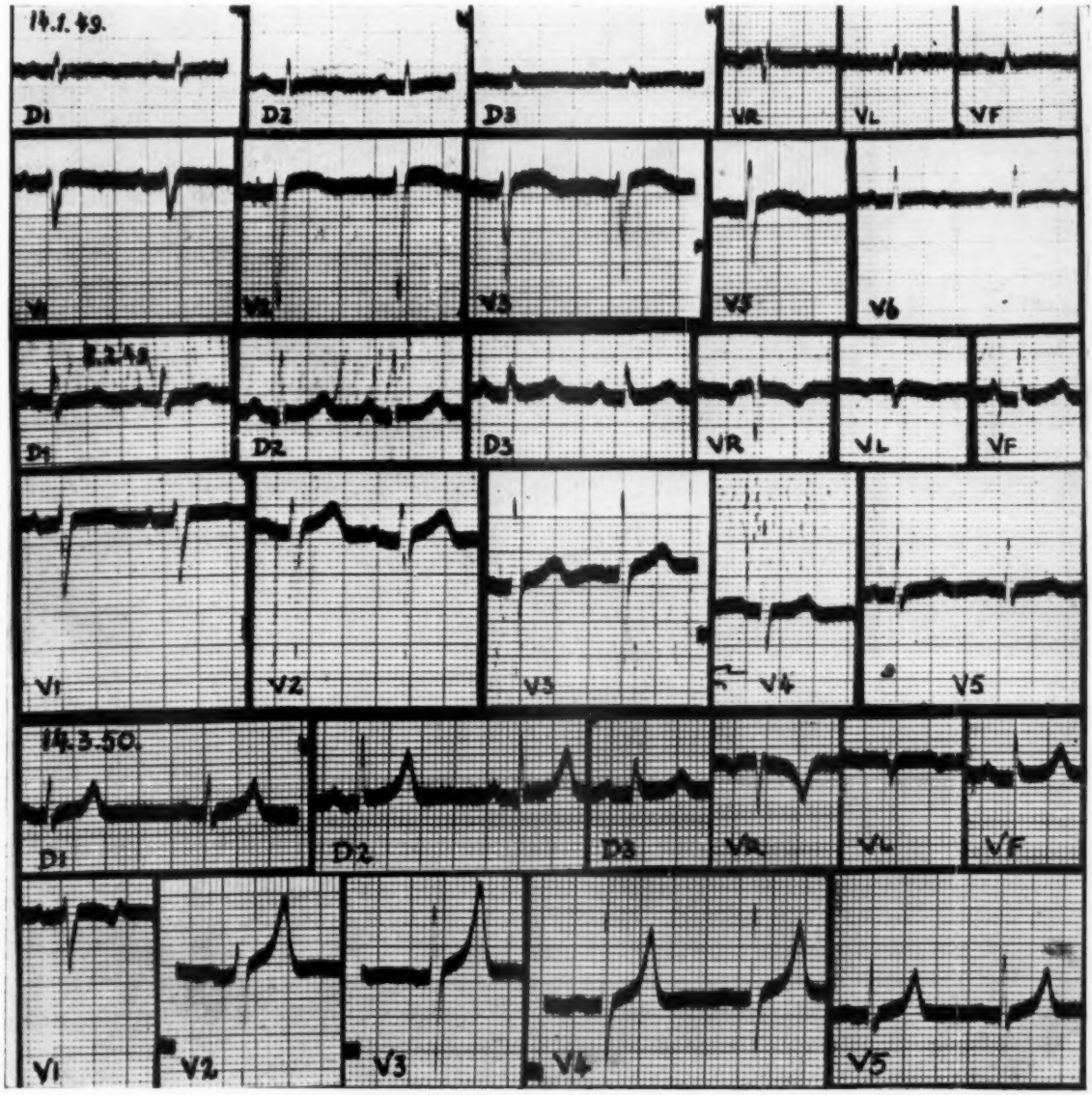

Fig. 6 (Case 4).—(J.V.C.)—Low voltage of the QRS complexes and flattened T waves in all leads. Three weeks later a definite increase in amplitude of all deflections is evident. The last tracing taken one year later shows very tall, peaked T waves both in standard and precordial leads.

hypertrophy, since they both determine the same pattern in precordial leads. Because of the persistent signs of left ventricular hypertrophy in the electrocardiogram (Fig. 8), it may be difficult occasionally to distinguish these cases from hypertensive heart disease, particularly in the presence of transient arterial hypertension, which is not an uncommon occurrence in beriberi heart disease. Conduction defects do not usually occur,[1,38] although a small number of isolated cases of doubtful interpretation have been published in the literature.[11,41] Experimentally, however, transient bundle branch block has been produced in chronically thiamine deficient rats.[42] In Case 21 the electrocardiogram revealed a complete left bundle branch block of the unusual type, with right axis deviation

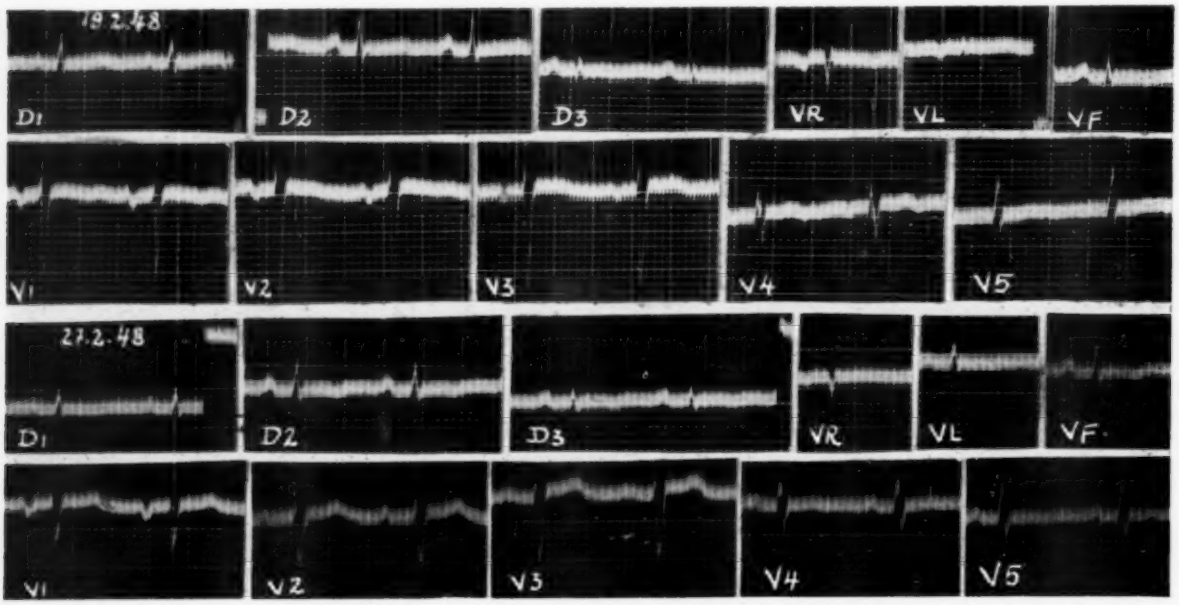

Fig. 7 (Case 9).—(A.F.)—Low voltage of the QRS complexes and T waves in all leads. The tracing remained unchanged after eight days of intensive thiamine treatment.

(Fig. 10). This patient was a 33-year-old man with a history of chronic alcoholism. The clinical diagnosis of cardiac beriberi was considered improbable in the presence of the conduction disturbance, of isolated left ventricular failure for several months as well as an initial episode of precordial pain.[27] At autopsy, however, the presumptive diagnosis of coronary sclerosis was entirely excluded, and the histologic picture was consistent with beriberi heart disease.

An interesting observation from the electrocardiographic standpoint is the fact that apparently normal tracings may show subsequent "improvement" after thiamine treatment. This was observed in three cases of our series (Cases 1, 6, and 19). Conversely, the T-wave inversion may become more marked as the patient improves clinically (Cases 2, 8, and 15) as illustrated in Fig. 9.

Diagnosis.—The diagnosis of beriberi heart disease is quite evident in the presence of the classical hyperkinetic syndrome associated with predominantly right-sided congestive heart failure. However, in the absence of a rapid circulation and in the presence of left-sided heart failure the clinical picture may resemble

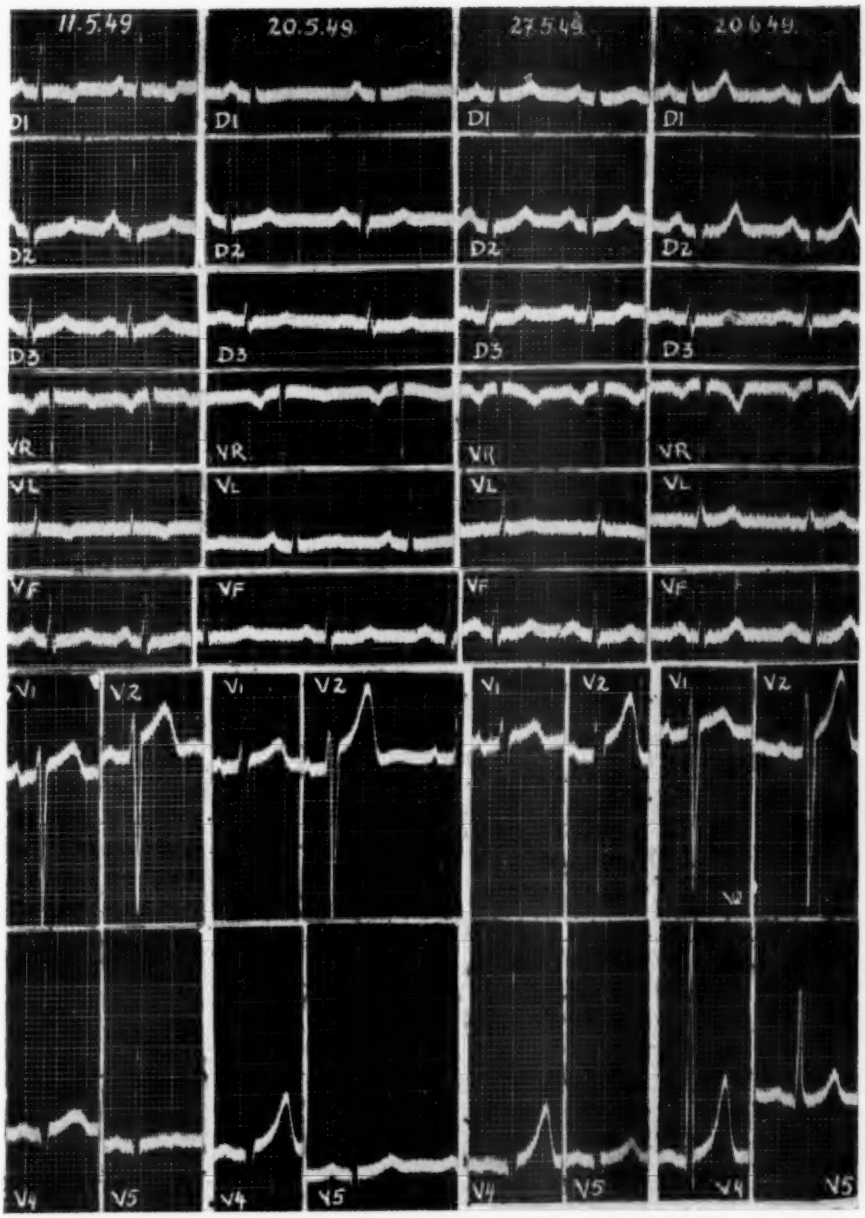

Fig. 8 (Case 3).—(R.G.F.)—The first record shows inverted T waves in Leads *I* and V_L, in addition to signs of left ventricular hypertrophy in the precordial leads. Nine days later, the T waves have become isoelectric in Leads *I* and V_L, positive in Lead V_5, and of increased amplitude in Leads V_2 and V_4. The tall R waves are still evident in the left precordial leads. The third tracing reveals apparent normalization of the T-wave changes. However, the last record shows a further increase in amplitude of the T waves.

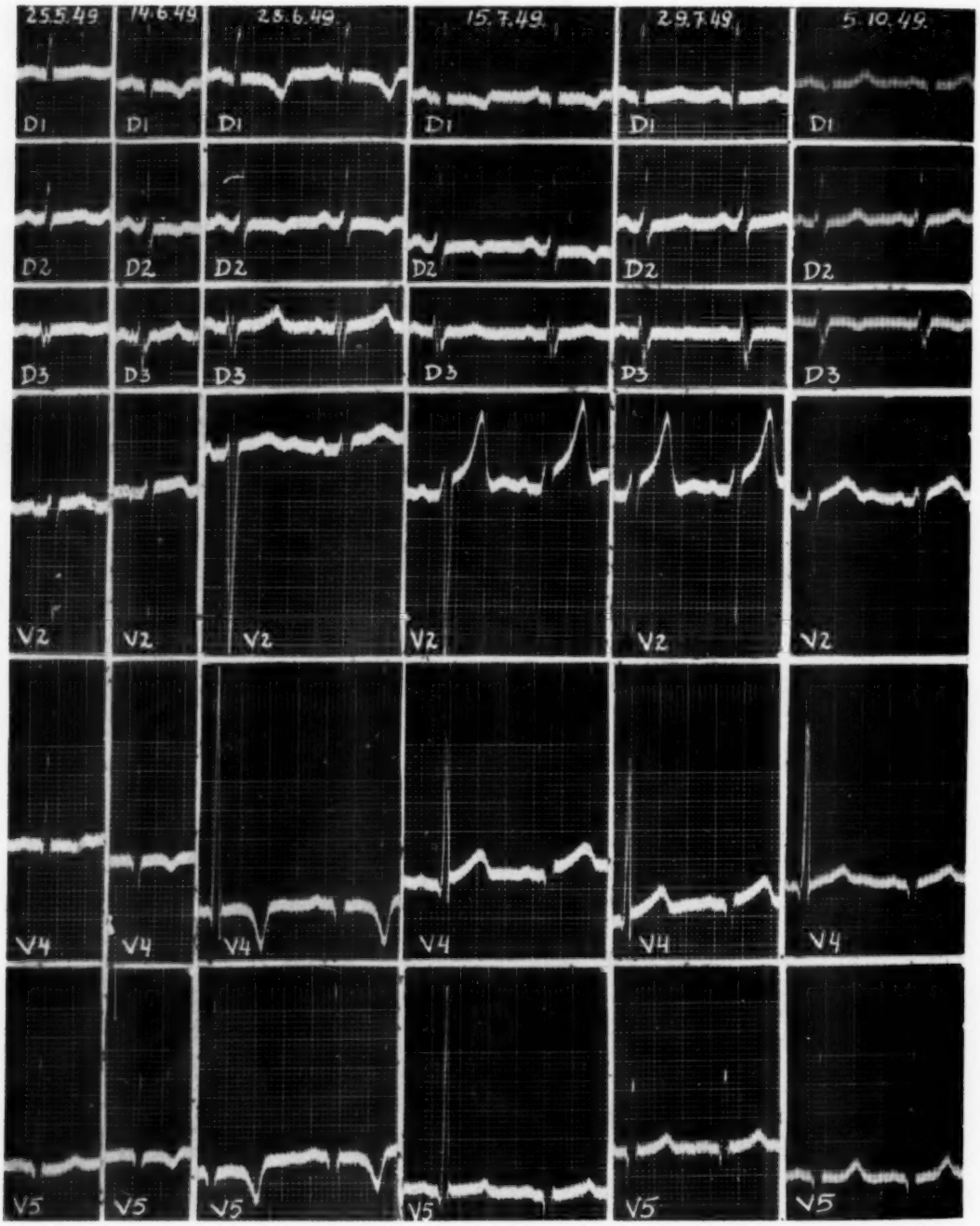

Fig. 9 (Case 8).—(C.O.S.)—The first electrocardiogram shows signs of left ventricular hypertrophy with flattened T waves in standard and left precordial leads. Twenty days later during convalescence from a severe bout of heart failure, the T waves have become inverted. Notwithstanding clinical improvement, the third tracing shows more acute T-wave inversion, with increased amplitude of the R waves in Leads V_4 and V_5. Subsequent tracings reveal progressive disappearance of the T-wave changes with signs of persistent although moderate left ventricular hypertrophy.

other more common types of degenerative heart disease, caused by hypertension or coronary sclerosis. It is important, therefore, to emphasize the significant diagnostic features of cardiac beriberi which may be summarized as follows: (1) a history of chronic alcoholism; (2) the presence of other signs of thiamine deficiency such as peripheral polyneuritis; (3) the lack of other etiologic factors of heart disease; (4) the favorable results of thiamine medication.

Although some of these features may occasionally be absent in the unusual cases of beriberi heart disease, the total clinical picture is sufficiently characteristic in most cases to lead to the correct diagnosis.

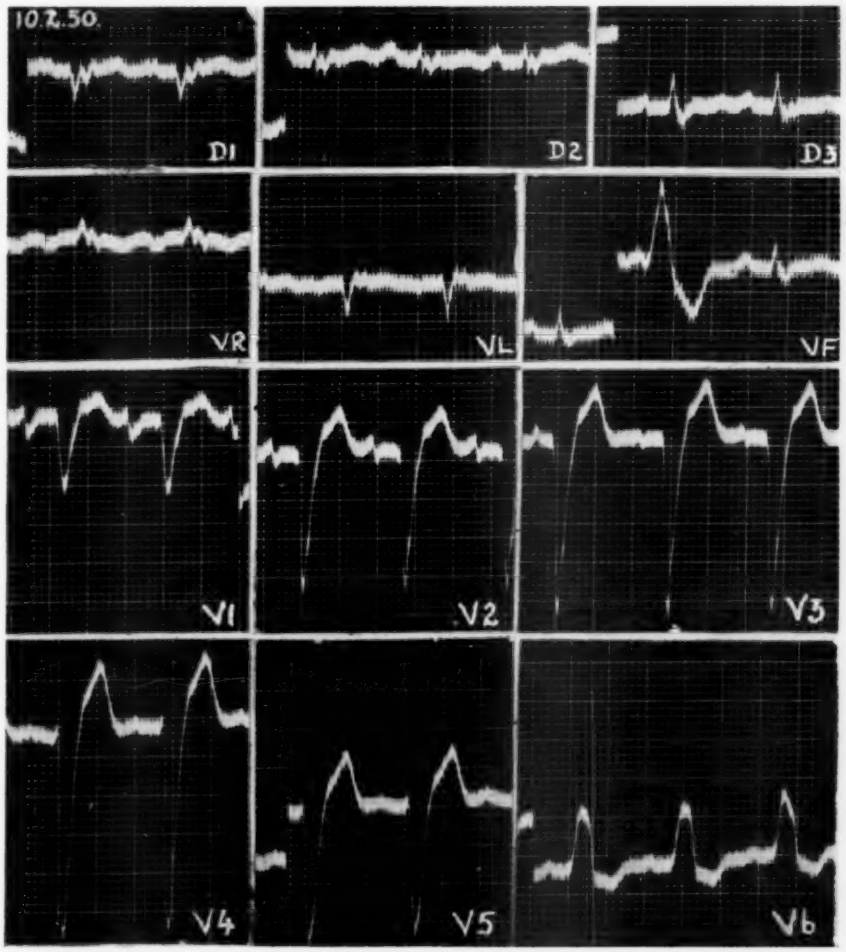

Fig. 10 (Case 21).—(D.V.)—Complete left bundle branch block with right-axis deviation. This case had autopsy confirmation.[27]

Clinical Course and Prognosis.—These are extremely variable, according to the degree and the duration of thiamine deficiency. Thus, chronic untreated thiamine deficiency may lead to progressive and irreversible changes in the heart muscle. The occurrence of other associated factors of cardiac disease constitutes aggravating conditions and usually determines an unfavorable prognosis.

Certain types of cardiac beriberi, with a sudden onset, may occur sporadically and have been described in the Orient as "Shoshin" or the so-called acute pernicious form of beriberi heart disease. In such cases the patients are usually in severe congestive failure, markedly cyanotic, and complain of precordial distress. Circulatory collapse generally occurs and may lead to death in a short period of time. These cases must be diagnosed readily, since the administration of thiamine may be a lifesaving procedure in the early stage of this condition. We have observed recently two patients with this clinical syndrome, one of which was in a desperate condition, showing no response to cardiotonic drugs, stimulants, etc., but improving dramatically and almost immediately after the intravenous administration of 100 mg. of thiamine.

Pathologic Findings.—In cardiac beriberi these usually consist of hypertrophy and dilatation, involving both the left and the right chambers of the heart. Hydropic degeneration of the myocardial fibers is usually present in addition to interstitial and intracellular edema. The myocardial changes in beriberi heart disease are usually reversible in the initial stages. In long-standing cases, however, these changes may become permanent as a result of progressive myocardial fibrosis which may be similar to that observed in other forms of degenerative heart disease.[27] An unusual type of cardiac fibrosis, involving the subendocardial aspects of both ventricles, associated with mural thrombosis, has been described in vitamin deficient patients[43,44] and was included among the heart diseases of unknown etiology. According to Smith and Furth[44] these cases probably represent unusual examples of cardiac beriberi, since it is suggested that myocardial fibrosis may result not only from chronic ischemia but also from a nutritional deficiency.

Among the six fatalities in our series, autopsy was obtained in five patients. Histologic examination revealed a marked degree of interstitial edema with dissociation of the myocardial fibers in three cases. Figures 11 and 12 illustrate typical examples of these findings, showing perivascular edema in one case (Fig. 11) which extended to the vessel wall.

Therapy.—From the therapeutic standpoint, although vitamin B_1 administered parenterally is considered the specific treatment for cardiac beriberi, it should be emphasized that some cases respond to bed rest, salt-free diet, digitalis, and mercurial diuretics. Therefore, the beneficial effects of these nonspecific measures should not rule out the diagnosis of thiamine deficiency. On the other hand, certain irreversible forms of cardiac beriberi may show only a slight improvement or no response at all to thiamine medication. In such cases, therefore, it is evident that the therapeutic response is not a necessary diagnostic feature of beriberi. The recognition of the deficiency factor as the cause of cardiac involvement in the advanced cases is seldom possible from the clinical standpoint, unless one is aware of the occurrence of this type of cardiac beriberi which so closely resembles arteriosclerotic and hypertensive heart disease.

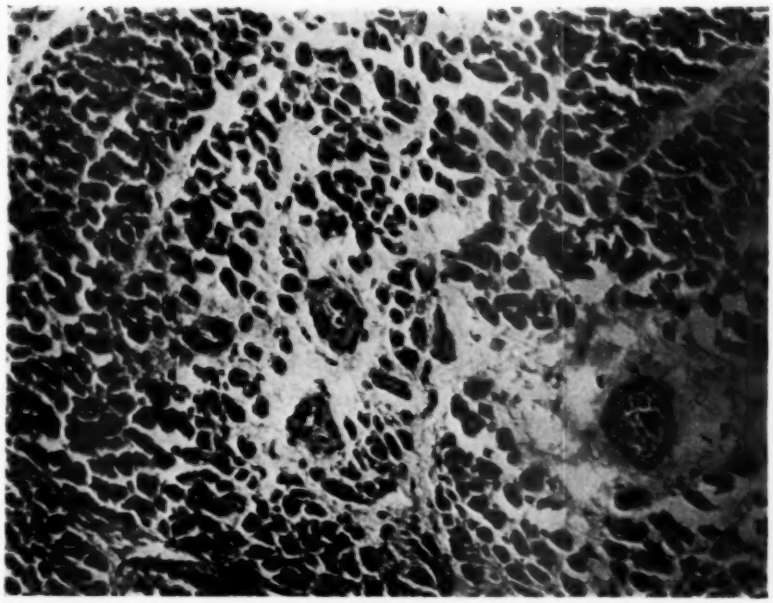

Fig. 11 (Case 17).—(L.A.A.)—Histologic section of the heart muscle from a patient with cardiac beriberi associated with congenital pulmonary valvular stenosis. Signs of serous myocarditis, with interstitial edema, dissociation of the myocardial fibers and edema of the vessel walls.

Fig. 12 (Case 9).—(A.F.)—Marked interstitial edema dissociating the myocardial fibers. The latter show occasional areas of necrosis.

SUMMARY

Beriberi heart disease seems to be a frequent condition in Brazil, as judged by the twenty-two cases which we have observed during a three-year period in the city of Rio de Janeiro. In most patients, beriberi was the only etiologic factor, but there were some instances of other associated cardiac conditions, notwithstanding the fact that the vitamin deficiency was the main cause in all cases. Chronic alcoholism was the major etiologic factor, since all patients in our series consumed large amounts of alcoholic beverages for prolonged periods of time.

All our patients were men and apparently well-nourished individuals.

Edema was the earliest and most frequent clinical manifestation. Variable degrees of dyspnea occurred in twenty cases during the course of cardiac failure, although it appeared as an initial symptom in two cases.

A certain lability of the pulse rate was an interesting feature, particularly a transient bradycardia which usually appeared at the onset of clinical improvement. Blood pressure variations were equally observed, particularly a transient hypertension during the course of heart failure. Clinical signs of polyneuritis were present in all but two cases and were rarely of clinical significance. The main roentgenologic and electrocardiographic features were analyzed, emphasizing their reversibility on thiamine treatment. The occasional diagnostic difficulties in distinguishing cardiac beriberi from hypertensive and arteriosclerotic heart disease were pointed out.

There were six deaths in the present series caused by heart failure. Five cases came to autopsy and were all confirmed as representing instances of thiamine deficiency.

Considering the fact that the unfavorable prognosis of beriberi heart disease in certain cases is due to the prolonged duration of thiamine deficiency leading to an irreversible myocardial fibrosis, the early recognition of this condition is emphasized, since appropriate therapeutic measures at this time may result in a complete cure.

REFERENCES

1. (a) Aalsmeer, W. C., and Wenckebach, K. F.: Herz und Kreislauf bei der Beri-beri Krankheit, Wein. Arch. inn. Med. **16**:193, 1929.
   (b) Wenckebach, K. F.: Das Beri-beri-Herz, Berlin, 1934, Julius Springer.
   (c) Wenckebach, K. F.: Heart and Circulation in a Tropical Avitaminosis. Second St. Cyres Lectures, Myocarditis, London, 1937, Eyre & Spottiswoode Publishers, Ltd.
2. Keefer, C. S.: The Beriberi Heart, Arch. Int. Med. **45**:1, 1930.
3. Shimazono, J.: Beriberi—*in* Stepp, W., and Györgyi, P.: Die Avitaminosen, Berlin, 1927, Julius Springer.
4. (a) Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in Vitamin Deficiency States, Tr. Am. Phys. **51**:341, 1936.
   (b) Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi), Ann. Int. Med. **11**:104, 1937.
   (c) Weiss, S.: Occidental Beriberi With Cardiovascular Manifestations—Its Relation to Thiamin Deficiency, J.A.M.A. **115**:832, 1940.
5. White, P. D.: Heart Disease, ed. 3, New York, 1944, The Macmillan Company.
6. Levine, S.: Clinical Heart Disease, ed, 3, Philadelphia, 1945, W. B. Saunders Company.
7. Fishberg, A.: Heart Failure, Philadelphia, 1940, Lea & Febiger.
8. Dressler, W.: Clinical Cardiology, New York, 1942, Paul B. Hoeber, Inc.
9. (a) Silva Lima: Ensaios sobre o Beriberi no Brasil. 1872.
   (b) Silva Lima: Contribuição para a historia de uma molestia que reina atualmente na Bahia sob a forma epidemica e caracterizada pela paralisia, edema e fraqueza geral. Gazeta Medica da Bahia, Nov., 1866.

10. (a) Almeida Magalhães: Das perturbações cardiacas no Beriberi. Brasil Medico. 1892-1893.
(b) Almeida Magalhães: O coração no Beriberi. Estudo clinico. Typ. Leuzinger, Rio de Janeiro, 1901.
11. (a) Blankenhorn, M. A.: The Diagnosis of Beriberi Heart Disease, Ann. Int. Med. **23**:398, 1948.
(b) Blankenhorn, M. A., Vilter, C. F., Scheinker, I. M., and Rustin, R. S.: Occidental Beriberi Heart Disease, J.A.M.A. **131**:717, 1946.
12. Gelfand, D., and Bellet, S.: Cardiovascular Manifestations of Beriberi, M. Clin. North America **33**:1643, 1949.
13. Benchimol, A. B., and Cotrim, M.: Coração beriberico, Arq. Clin. **4**:182, 1947.
14. Siqueira, R., and e Segadas, R.: Algumas considerações clinicas sobre a importancia da hipovitaminose B_1 em patologia cardiovascular, Hospital **18**:944, 1940.
15. Fraga Filho, C., Jr., and Vaissman, I.: Distúrbios cardiovasculares na hipovitaminose B_1, Resenha Clín. cient. **18**:123, 1949.
16. Schermann, J., and Benchimol, A. B.: Hipovitaminose B_1 e cardiopatia associada. Papel do alcool e efeitos beneficos da terapeutica aneurinica, Med. cir. pharm. **55**:1, 1940.
17. Lecoq, R.: Les vitamines B dans leur rapports avec les glucides, les protides et les lipides du regime, Paris, 1935, Vigot Freres.
18. Abderhalden, E., and Wertheimer, F.: Beziehungen des Vitamins B Komplexes (Misbezonders des Vitamins B_1) zum Kohlehydrathaushalt, Arch. f. d. ges. Physiol. **233**:395, 1933.
19. Castro, F.: Boletins da Imperial Academia de Medicina, **53**:1886.
20. Kepler, E. S.: Beriberi From a Diet of Raw Starch, J.A.M.A. **85**:409, 1925.
21. Scott, R. C., and Hermann, G. R.: Beriberi (Maladie des jambes) in Louisiana With Reference to Cardiac Manifestations, J.A.M.A. **90**:2083, 1928.
22. Miura, L.: Beriberi oder Kakke, Ergebn. d. inn. Med. u. Kinderh. **4**:280, 1909.
23. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, ed. 2, Springfield, Ill., 1943, Charles C Thomas.
24. Epstein, S.: Observations on Beriberi Heart Disease, Am. Heart J. **34**:432, 1947.
25. Swan, W. G. A., and Laws, F.: A Case of Beriberi Heart, Brit. Heart J. **2**:241, 1940.
26. Hashimoto, H.: Acute Pernicious Form of Beriberi and Its Treatment by Intravenous Administration of Vitamin B_1 With Special Reference to Electrocardiographic Changes, Am. Heart J. **13**:581, 1937.
27. Schlesinger, P., and Benchimol, A. B.: Cardiac Beriberi Simulating Arteriosclerotic Heart Disease, Am. Heart J. **42**:801, 1951.
28. Dustin, C. C., Weyler, H., and Roberts, C. P.: Electrocardiographic Changes in Vitamin B_1 Deficiency, New England J. Med. **220**:15, 1939.
29. Konstam, G., and Sinclair, H. M.: Cardiovascular Disturbances Caused by Deficiency of Vitamin B_1, Brit. Heart J. **2**:231, 1940.
30. Boyd Campbell, S. B., and Allison, R. S.: Pellagra, Polyneuritis and Beriberi Heart, Lancet **1**:738, 1940.
31. Jolliffe, N., and Goodhart, R.: Beriberi in Alcohol Addicts, J.A.M.A. **111**:380, 1938.
32. Morgan Jones, A., and Bramwell, C.: Alcoholic Beriberi Heart, Brit. Heart J. **1**:188, 1939.
33. Pazzanese, D.: Modificações de forma do electrocardiograma, Grafica da Pref. de São Paulo, 1942.
34. Drury, A. N., Harris, L. J., and Mandsley, C.: Vitamin B Deficiency in the Rat. Bradycardia as a Distinctive Feature, Biochem. J. **24**:1632, 1930.
35. Zoll, P. M., and Weiss, S.: Electrocardiographic Changes in Rats Deficient in Vitamin B_1, Proc. Soc. Exper. Biol. & Med. **35**:259, 1936.
36. Soldati, L.: Los transtornos circulatorios de la Avitaminosis B_1, Buenos Aires, 1940, B. El Ateneo.
37. Porter, W.: The Heart and Deficiency Diseases. Modern Concepts of Cardiovascular Diseases, Am. Heart Assoc., New York, Vol. III, No. 9, Sept., 1934.
38. Schretzenmayer, A.: Roentgenologische und Elektrokardiographische Studien an Beriberi Herzens, Arch. Schiffs. u. Tropenhyg. **43**:427, 1939.
39. Van Bogaert, L.: Beriberi alcoholique, Arch. d. mal. du. coeur **31**:1195, 1938.
40. Goodhart, A., and Joliffe, N.: The Role of Nutritional Deficiencies in the Production of Cardiovascular Disturbances in the Alcohol Addict, Am. Heart J. **15**:569, 1938.
41. Braun, K., Roth, I., and Suesskind, S.: Intraventricular Block in Malnutrition and Vitamin B Deficiency. A Report of Two Cases in Children, J. Pediat. **30**:177, 1947.
42. Hundley, J. H., Ashburn, L. L., and Sebrell, W. H.: The Electrocardiogram in Chronic Thiamine Deficiency in Rats, Am. J. Physiol. **144**:404, 1945.
43. Dock, W.: Marked Cardiac Hypertrophy and Mural Thrombosis in Beriberi Heart, Tr. A. Am. Physicians **35**:61, 1940.
44. Smith, J. J., and Furth, J.: Fibrosis of the Endocardium and the Myocardium With Mural Thrombosis. Notes on Its Relation to Isolated (Fiedler's) Myocarditis and to Beriberi Heart, Arch. Int. Med. **71**:602, 1943.
45. Garland, L. H., and MacKenney, A. C.: Roentgen Diagnosis of Vitamin Deficiency Cardiac Conditions With Some Clinical Observations on Thiamin Deficiency, Radiology **38**:426, 1942.

NORMAL PRESSURE IN THE RIGHT HEART AND PULMONARY ARTERY

NOBLE O. FOWLER, M.D., RICHARD N. WESTCOTT, M.D., AND RALPH C. SCOTT, M.D.

CINCINNATI, OHIO

IN 1941, Cournand and Ranges[1] introduced the technique of catheterization of the right heart in man. Since this time, there have been published a large number of papers testifying to the usefulness of the method in physiologic and diagnostic investigations. In the years since 1941, several reports have appeared in the medical literature, describing normal values of pressures in the right heart and pulmonary artery in small groups of subjects.[2-7] With the more widespread employment of cardiac catheterization as an increasing number of congenital and acquired cardiac defects are becoming amenable to operation, it seems to be essential to establish the normal range of these pressures in as large a group of subjects as can be accumulated. Accordingly, we have described below our findings of pressures in the right heart and pulmonary artery in eighteen normal subjects and have reviewed the findings of others who have published data obtained from groups of normal individuals.

MATERIAL

The material consisted of eighteen convalescent patients from the medical wards of the Cincinnati General Hospital. Their ages ranged from eighteen to sixty-six years. These subjects were free from cardiac disease as indicated by physical examination, roentgenogram, and electrocardiogram. The subjects also had lungs which were normal to roentgenogram except for one who was convalescent from a small lung abscess.

METHOD

Catheterization of the right heart was performed in the manner of Cournand and Ranges.[1] Patients were studied in the fasting state, sedated by 0.1 Gm. of Seconal Sodium. Pressures were recorded by strain gauges and a five-channel optical oscillograph (Hathaway). Ten centimeters upward from the spine of the recumbent subject was used as a zero level. Pressures were measured over two or more respiratory cycles. Mean pressures were obtained by planimetry. Pulmonary "capillary" pressures were determined in the manner of Hellems and associates.[8]

From the Cardiac Laboratory, Cincinnati General Hospital, the Cardiac Laboratory, Brooklyn Hospital, and the Department of Medicine, State University of New York at New York City.

Supported in part by the Joseph May Fund, Brooklyn Hospital.

Received for publication March 19, 1953.

RESULTS AND DISCUSSION

The values found for the various pressures in the right side of the heart in our study and in those of others are summarized in Table I. Our values for right atrial pressure, averaging 2.9 mm. Hg for the mean pressure, agree closely with those of Lagerlöf and Werkö,[7] whose values for normal right atrial pressure averaged 2.75 mm. Hg. The values given for this determination by Bloomfield and co-workers[2] were slightly lower, possibly because of a different zero level. The values obtained by Hickam and Cargill[6] are also a bit lower than ours. We have given also in Table I the values obtained for the a, x, c, x′, v, and y waves of the right atrial pressure pulse.

TABLE I. NORMAL RIGHT HEART AND PULMONARY ARTERY PRESSURES

AUTHOR	LAGERLÖF AND WERKÖ	BLOOMFIELD AND ASSOCIATES	BORDEN	DEXTER AND ASSOCIATES	FOWLER AND ASSOCIATES	HICKAM AND CARGILL
Rt. Atrium						
Av. Mean	2.75(13)*	0.11(9)			2.9(11)	0.8(6)
Range	1 to 5	−2 to +2			1 to 4.5	0 to 4
S. D.					1.22	
a wave					5.6(9)	
Range					2.5 to 7.0	
x wave					2.9(7)	
Range					1 to 5.5	
c wave					3.8(5)	
Range					1.5 to 6.0	
x′ wave					1.7(8)	
Range					0 to 5.0	
v wave					4.6(7)	
Range					2 to 7.5	
y wave					2.4(7)	
Range					0 to 5.5	
Rt. Ventricle						
Peak Systole	24(13)	25(13)			25.6(7)	
Range	17 to 30	18 to 30			19 to 31.5	
End Diastole	4(13)	2.7			3.6(7)	
Range	1 to 7	−0.5 to 4.5			2 to 6.0	
Pulm. Artery						
Av. Mean	15(13)			15(8)	14.4(18)	11(8)
Range	9 to 19			13 to 17	10 to 18	8 to 14
S. D.					2.63	
Peak Systole	23(13)		20.1(12)	23(8)	22.9(18)	
Range	14 to 29		11 to 26	19 to 26	16 to 29	
S. D.			3.7		3.65	
End Diastole	8(13)		8.8(12)	9(8)	9.1(18)	
Range	4 to 11		5 to 11	6 to 12	5 to 13	
S. D.			1.2		2.54	
Dicrotic					13.4(14)	
Notch					8 to 18.5	
Pulm. "Capillary"						
Av. Mean				9(8)	8.4(16)	
Range				6 to 12	4.5 to 13	
S. D.					2.11	

Pressures are expressed in mm. Hg.
*Figures in parentheses indicate the number of subjects studied.

Our values for right ventricular pressures were similar to those of Bloomfield and co-workers,[2] and to those of Lagerlöf and Werkö,[7] averaging 25.6 mm. Hg in systole and 3.6 mm. Hg in diastole. Our average mean pulmonary arterial pressure of 14.4 mm. Hg was essentially the same as the 15 mm. Hg average obtained by Dexter and associates,[4] and the 15 mm. Hg figure obtained by Lagerlöf and Werkö,[7] although the range in our data (10 to 18 mm.) and in those of Lagerlöf and Werkö (9 to 19 mm.) was larger than in those of Dexter and associates (13 to 17 mm.). This may well be due to the fact that the last group of workers studied a smaller number of subjects. The mean pulmonary arterial pressures obtained by Hickam and Cargill[6] were slightly lower than those cited above. Our own values for pulmonary arterial systolic pressures were essentially the same as those found by Lagerlöf and Werkö,[7] our range being 16 to 29 mm. Hg, and theirs being 14 to 29 mm. Hg. Borden[3] had somewhat lower range limits for this pressure. Our values for diastolic pressure in the pulmonary artery were from 5 to 13 mm. Hg; these were essentially the same as those found by Borden,[3] Dexter and co-workers,[4] and by Lagerlöf and Werkö.[7]

The values we found for pulmonary "capillary" pressure were from 4.5 to 13 mm. Hg, a slightly wider range than the 6 to 12 mm. Hg found by Dexter and associates[4] and somewhat higher than the 2.5 to 8.5 mm. Hg found in eight normal subjects by Doyle and co-workers.[5] We have not included the values given by Doyle in our table because both his pulmonary arterial and pulmonary "capillary" pressures are considerably lower than those reported by other workers, suggesting a systematic difference in technique of measurement.

Although most of the subjects included in the above studies were considered under basal conditions, some had had a light breakfast. This probably did not influence the pressure determinations, since Hickam and Cargill[6] showed that even light exercise does not elevate significantly pressures in the right side of the heart and pulmonary artery of normal individuals. It is hoped that the above will be of aid in indicating the normal range limits to workers in the field of cardiac catheterization. It should be emphasized that the studies summarized here have been made on adults. Limited experience suggests that normal pressures in the right side of the heart and pulmonary artery of the older child are not greatly different from these.

SUMMARY

A study of pressures in the right side of the heart and pulmonary artery of eighteen normal subjects of our own and a review of the findings of other authors in a total of 54 additional subjects indicated the following range limits of normal pressure in mm. Hg.

1. Right atrial mean pressure: −2 to +5.
2. Right ventricle: systole, 17 to 31.5; end diastole, −0.5 to +7.
3. Pulmonary artery: systole, 11 to 29; diastole, 4 to 13; mean, 8 to 19.
4. Pulmonary "capillary": mean, 5 to 13.

REFERENCES

1. Cournand, A., and Ranges, H. A.: Catheterization of the Right Auricle in Man, Proc. Soc. Exper. Biol. & Med. **46**:462, 1941.
2. Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W., Jr.: Recording of Right Heart Pressures in Normal Subjects and in Patients With Chronic Pulmonary Disease and Various Types of Cardio-Circulatory Disease, J. Clin. Investigation **25**:693, 1946.
3. Borden, C.: Fundamental and Clinical Aspects of Pulmonary Hypertension, Minnesota Med. **31**:1216, 1948.
4. Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B. G., Goodale, W. T., and Hellems, H. K.: Studies of the Pulmonary Circulation in Man at Rest. Normal Variations and Inter-relations Between Increased Pulmonary Blood Flow, Elevated Pulmonary Arterial Pressure, and High Pulmonary "Capillary" Pressures, J. Clin. Investigation **29**:602, 1950.
5. Doyle, J. T., Wilson, J. S., and Warren, J. V.: The Pulmonary Vascular Responses to Short Term Hypoxia in Human Subjects, Circulation **5**:263, 1952.
6. Hickam, J. B., and Cargill, W. H.: Effect of Exercise on Cardiac Output and Pulmonary Artery Pressure in Normal Persons and in Patients With Cardiovascular Disease and Pulmonary Emphysema, J. Clin. Investigation **27**:10, 1948.
7. Lagerlöf, H., and Werkö, L.: Studies on the Circulation in Man. II. Normal Values for Cardiac Output and Pressure in the Right Auricle, Right Ventricle, and Pulmonary Artery, Acta physiol. Scandinav. **16**:75, 1948.
8. Hellems, H. K., Haynes, F. W., and Dexter, L.: Pulmonary "Capillary" Pressure in Man, J. Appl. Physiol. **2**:24, 1949.

THE EFFECT OF POSTURE AND ADRENERGIC BLOCKADE WITH DIBENZYLINE ON RENAL HEMODYNAMICS AND EXCRETION OF WATER AND ELECTROLYTES IN PATIENTS WITH HYPERTENSION WITH AND WITHOUT RENAL DAMAGE

RALPH V. FORD, M.D., JOHN H. MOYER, M.D., AND CHARLES L. SPURR, M.D.
WITH THE TECHNICAL ASSISTANCE OF R. M. WELLER AND C. P. SMITH

HOUSTON, TEXAS

DIBENZYLINE* (N-phenoxy-isopropyl-N-benzyl-β-chlorethylamine HCl) has been subjected to fairly extensive clinical investigation in the treatment of hypertension.[1-3] The drug is a potent adrenergic blocking agent and is effective orally.[4] However, the renal hemodynamic effects of blood pressure reduction with this agent have not been evaluated. In addition to the renal response to blood pressure reduction, this drug affords us a means of evaluating the effect of adrenergic blockade on renal hemodynamics in the recumbent position and when the body is under stress in the upright position in patients with hypertension. The data indicate that, in spite of the reduction in blood pressure, complete renal hemodynamic adjustment occurs in the recumbent position. The depression of renal blood flow and glomerular filtration rate which occurs in the untreated patient following head-up tilting is not altered by adrenergic blockade with this agent. In addition, tilting of the hypertensive patient appears to depress water and sodium excretion out of proportion to the reduction in glomerular filtration rate, quite similar to the response of normal individuals. This response is also not affected by adrenergic blockade with Dibenzyline.

METHODS

Twelve men patients with hypertension of varied types were studied by measurements of glomerular filtration rate (inulin clearance), renal plasma flow (para-aminohippurate clearance), and maximum tubular excretory capacity (TmPAH). The rates of urine formation, sodium excretion, potassium excretion, and changes in blood pressure were observed. The techniques of renal function and the methods of analysis have been previously described.[5]

Control determinations of glomerular filtration rate and renal plasma flow consisted of two consecutive 10 minute periods in recumbency followed by two consecutive 10 minute periods in the 60 degree caudally tilted position. The

From the Departments of Medicine and Pharmacology of the Baylor University College of Medicine and the Medical Research Laboratory of the Veterans Administration Hospital, Houston, Texas.
Received for publication March 23, 1953.

*Furnished by Smith, Kline, & French Laboratories.

patient was then returned to the recumbent position and, after a 30 minute equilibration period, glomerular filtration rate and maximum tubular excretory capacity were determined in the recumbent (2 periods) and in the 60-degree tilted position (2 periods). The patients were restudied after 2 to 7 days, during which time the patient was given oral Dibenzyline in an incremental fashion in order to establish adrenergic blockade. The average single dose required to establish blockade was 95 mg. The postdrug studies were done in precisely the same fashion as during the control period, recumbent and tilted. Adrenergic blockade was proved by norepinephrine unresponsiveness (complete blockade) at the time of the drug study. Thus, twice the dose of norepinephrine, which produced a rise of at least 40 mm. Hg systolic pressure in the control period, was injected during the drug study and found to produce no rise in blood pressure. Five of the patients were studied again in the same manner after 28 days of blockade.

RESULTS

The Effect of Renal Damage.—In order to evaluate the relationship of renal impairment to renal hemodynamic changes, these patients have been arbitrarily divided into two groups on the basis of the control value for glomerular filtration rate.[6] Five patients with glomerular filtration rate less than 60 ml./min. were considered as having moderate to marked renal damage and were placed in Group A. Seven patients with glomerular filtration rate of more than 60 ml./min. were placed in Group B and were considered to have normal to minimally impaired renal function. There was no significant difference between the two groups in renal hemodynamic response to tilt or to adrenergic blockade.

The Effect of Adrenergic Blockade on Renal Functions.—The average mean blood pressure after adrenergic blockade dropped to 90 per cent of control in the recumbent position and to 78 per cent in the tilt. Despite the reduction in blood pressure in the recumbent position, renal plasma flow (Table II) was not significantly altered due to a decrease in renal vascular resistance (since hematocrit did not change). There was no change in maximum tubular excretory capacity of para-aminohippurate, indicating that the number of functioning nephrons did not change. Since the number of functioning glomeruli was not altered, the constancy of glomerular filtration rate indicates that no change (Table I) occurred in the filtration in the individual glomeruli. After adrenergic blockade, the tilted position produced a significant decrease in all renal functions. The capacity for the tubules to excrete para-aminohippurate was depressed less than glomerular filtration rate, indicating a decreased number of active nephrons as well as a decrease in filtration in the glomeruli continuing to function.

The Effect of Adrenergic Blockade on Water and Electrolyte Excretion.—Adrenergic blockade did not appear to consistently alter the excretion of water, sodium, and potassium in the recumbent position. However, acute tilt studies indicated that the rate of electrolyte excretion was consistently depressed more than renal functions.

Statistical Analysis.—Application of "t" tests to the paired differences (Table IV) showed that the fall in blood pressure in the supine position during adrenergic

TABLE I. EFFECT OF ADRENERGIC BLOCKADE ON RENAL FUNCTIONS

	PT.	DX.	MBP			GFR (INULIN)			GFR (CREATININE)			TmPAH		
			C	D	DT	C	D	DT	C	D	DT	C	D	DT
Group A	O. G.	GS.	165	125	121	27	32	27	32	42	32	25	27	31
	S. P.	NS.	156	133	117	38	40	26	34	39	27	30	25	20
	H. E.	GN.	117	106	109	45	32	27	50	34	29	43	44	42
	A. L.	NS.	134	117	78	48	44	32	43	42	30	48	36	28
	R. U.	NS.	130	130	107	55	62	54	74	93	88	51	51	54
	Subaverage		140	122	106	43	42	33	47	50	41	39	37	35
	Average % control			88	76		100	79		108	85		94	91
Group B	M. I.	NS.	147	138	117	70	73	35	74	65	37	59	63	40
	B. E.	NS.	135	128	119	85	54	56	80	51	48	55	52	48
	M. C.	EH.	129	124	108	95	88	73	97	85	73	91	90	83
	I. N.	EH.	140	91	75	96	95	67	95	99	70	64	73	67
	A. D.	EH.	136	120	108	122	149	153	133	126	115	95	94	84
	A. T.	EH.	143	141	102	115	88	65	113	89	59	74	80	56
	M. U.	NS.	139	138	136	75	90	42	71	100	58	53	52	51
	Subaverage		138	126	109	94	91	70	95	88	66	70	72	61
	Average % control			91	79		97	72		94	68		103	87
	Grand average		139	124	108	73	71	55	75	72	56	57	57	50
	Average % control			90	78		98	75		100	75		99	89
	P			***	***		n.s.	***		n.s.	***		n.s.	*

MBP—Mean Blood Pressure = Diastolic Pressure + $\frac{\text{Pulse Pressure}}{3}$
GFR—Glomerular Filtration Rate
RPF—Renal Plasma Flow—PAH Clearance
TmPAH—Maximum Tubular Excretory Capacity for PAH
Pt—Patient
Dx—Diagnosis
GS—Glomerulosclerosis
NS—Nephrosclerosis
GN—Glomerulonephritis
EH—Essential Hypertension
C—Control
D—With Drug
DT—Tilt After Drug

P = <0.05–*
= <0.01–***
= significant levels

TABLE II. THE EFFECT OF ADRENERGIC BLOCKADE AND TILTING ON RENAL VASCULAR RESISTANCE

PT.	RPF			RBF			RENAL VASCULAR RESISTANCE				
	C	D	DT	C	D	DT	C	D	%D	DT	%T
Group A, O. G	100	146	107	150	220	160	1.10	0.572	52	0.767	70
S. P.	214	180	109	340	286	170	0.465	0.462	99	0.698	150
H. E.	376	478	317	530	680	450	0.228	0.160	70	0.299	131
A. L.	380	300	189	630	500	300	0.219	0.230	105	0.268	122
R. U.	515	413	396	800	680	610	0.169	0.210	124	0.182	108
Subaverage	317	303	224	490	473	338	0.436	0.327	90	0.443	116
% Control		103	74		105	73		90	90	116	116
Group B, M. I.	340	275	153	680	570	340	0.219	0.240	110	0.346	158
B. E.	334	648	490	610	1030	830	0.288	0.122	42	0.149	52
M. C.	564	546	505	830	800	750	0.164	0.152	93	0.148	90
I. N.	770	666	495	1410	1130	890	0.106	0.082	77	0.087	82
A. D.	1060	1030	1002	2050	1650	1550	0.066	0.073	111	0.070	106
A. T.	457	385	199	810	650	340	0.175	0.217	124	0.300	171
M. U.	371	522	310	640	870	510	0.219	0.158	72	0.268	122
Subaverage	557	582	451	1004	957	744	0.177	0.149	90	0.195	112
% Control		111	81		104	77		90	90	112	112
Average (12 pts.)	457	466	356	790	756	575	0.285	0.223	90	0.299	114
Average % control (12 pts.)		108	78		104	75		90	90	114	114
P		n.s.	***		n.s.	***		n.s.		**	

See Table I for key to abbreviations.

%D = D/C x 100
%T = DT/C x 100

RBF = Renal Blood Flow = RPF/1–Hematocrit
Renal Vascular Resistance = MBP/RBF
**P < 0.02

TABLE III. EFFECT OF ADRENERGIC BLOCKADE ON WATER AND ELECTROLYTE EXCRETION*

PT.	U.V.			Na			K		
	C	D	DT	C	D	DT	C	D	DT
S. P.	6.4	5.4	3.8	12.6	14.4	2.3	2.9	2.4	1.7
R. U.	8.3	5.0	4.1	5.0	9.9	6.1	9.2	2.3	2.0
B. E.	11.1	6.5	6.9	2.3	1.8	0.6	3.0	2.7	2.0
M. C.	7.9	1.9	1.1	17.9	6.5	2.5	3.0	0.7	0.6
A. D.	4.3	4.8	3.9	8.7	8.7	7.1	4.1	4.1	3.3
A. T.	8.4	11.0	3.2	10.9	3.3	0.1	5.4	3.8	1.7
M. U.	7.0	7.7	4.1	13.1	17.3	6.0	7.1	6.6	3.3
Average	7.6	6.0	3.9	10.1	8.8	3.5	5.0	3.2	2.1
Average % of Control		83	53		98	45		69	46

U.V.—Urine volume (ml./min.)
Na—Excretion of sodium (mg./min.)
K—Excretion of potassium (mg./min.)
Average % of Control = Average of individual changes over control (C)
*See Table I for key to abbreviations.

TABLE IV. STATISTICAL ANALYSIS**

FUNCTION	PERIODS COMPARED	MEAN DIFFERENCE ± STANDARD ERROR	T	P*
MBP	C – D	− 15 ± 4.44	3.341	<0.01
GFR (Inulin)	C – D	− 5.58 ± 5.56	0.988	n.s.
	D – DT	− 15.8 ± 4.55	3.479	<0.01
	CT – DT	0.417 ± 4.46	0.094	n.s.
GFR (Creatinine)	C – D	− 5.83 ± 6.23	0.9357	n.s.
	D – DT	− 16.58 ± 3.59	4.618	<0.01
	CT – DT	2.5 ± 4.85	0.515	n.s.
RPF	C – D	8.917 ± 36.2	0.246	n.s.
	D – DT	−109.75 ± 19.74	5.56	<0.01
	CT – DT	− 0.417 ± 31.5	0.01	n.s.
RVR	C – D	− 0.625 ± .454	1.377	n.s.
	D – DT	0.753 ± 0.043	3.096	<0.02
	CT – DT	0.028 ± 0.0259	1.095	n.s.
TmPAH	C – D	0.833 ± 1.15	0.724	n.s.
	D – DT	− 6.917 ± 2.54	2.738	<0.05
	CT – DT	3.5 ± 2.59	1.351	n.s.
U.V.	C – D	− 0.317 ± 1.716	0.185	n.s.
	D – DT	− 3.34 ± 0.995	3.357	<0.01
	CT – DT	− 0.292 ± 0.590	0.491	n.s.

*n.s. = Mean difference not statistically significant
p value of <0.01 means less than 1 chance in 100 that the observed difference was due to chance.
p = <0.02 and p = <0.05, as above; chances are 1 in 50 and 1 in 20, respectively.
**Statistical analysis through courtesy of H. E. Rockwell of Smith, Kline, & French Laboratories.
C—control
D—after Dibenzyline
CT—tilt before adrenergic blockade with Dibenzyline
DT—tilt after adrenergic blockade with Dibenzyline

blockade was highly significant statistically ($p < 0.01$). In the tilted position, the decrease in maximum tubular excretory capacity was significant at the five per cent level; in glomerular filtration rate, renal plasma flow, and urine volume, at the one per cent level. The effect of tilting on these functions after blockade did not differ significantly from that observed during the control studies.

Chronic Studies.—No changes were observed in the response to tilting after one month of adrenergic blockade in the five patients so studied. There was no significant change in renal function and electrolyte excretion to suggest renal toxicity of the drug.

DISCUSSION

Dibenzyline taken orally produces at least a partial adrenergic blockade as indicated by the failure to elicit a vasopressor response to intravenous norepinephrine. This effect has been used to examine certain features of renal hemodynamics. The lack of depression of renal function despite depression of blood pressure in the recumbent position after adrenergic blockade suggests that a decrease in renal vascular resistance has occurred. This might be accounted for by renal autonomy or by reduction in renal vascular resistance due to adrenergic blockade which was equivalent in the kidney to that in other areas of the body. The absence of an increase in renal blood flow is evidence against a specific renal effect.

Tilting produces certain undesirable changes in renal hemodynamics in hypertensive patients (also in normal persons) which are not altered by adrenergic blockade. Associated with an increase in renal vascular resistance, there is a depression of renal blood flow equivalent to or greater than the drop in blood pressure associated with a depression in glomerular filtration rate. A larger study[7] of twenty hypertensive patients was previously done in order to evaluate the hemodynamic effects of tilting alone. This furnished data which may be compared with those obtained from the patients in the present study. The data in Table II summarizes the changes in renal vascular resistance produced by adrenergic blockade in the supine position and compares this response to the tilted position. Table V compares the changes due to tilting alone (CT) and

TABLE V. THE EFFECT OF TILTING, BEFORE AND AFTER ADRENERGIC BLOCKADE

	MBP‡	GFR‡	RPF‡	TmPAH‡	U.V.‡	Na‡	K‡
**Control	141	80	435	59	8.6	9.7	3.1
Tilt Alone	126	51*	294*	47*	4.1*	3.5*	1.8*
% Control	90	71	72	82	50	40	75
**Control	139	73	457	57	7.1	11.4	5.3
Tilt Blockade	108*	55*	356*	70*	4.0*	4.3*	2.1*
% Control	78	75	78	89	53	45	46

‡Average values

*Statistically significant

**The control tilt alone comprises 20 patients. Twelve of these patients were also studied under adrenergic blockade, thus the average of the control values differs.

tilting following adrenergic blockade (DT). It will be seen that there is no significant (statistical) difference in the two groups except for a greater depression in blood pressure after adrenergic blockade.

The renal vascular response to tilting may be analogous to stress situations in general. Head-up tilting apparently inaugurates a sequence of generalized vasoconstrictive reflexes in order to maintain homeostasis. The kidney apparently participates in this vasoconstriction since there is a depression of all renal functions with decreased filtration in a decreased number of nephrons. Observations, following supposedly increased sympathetic activity, as by sciatic nerve stimulation,[9] renal plexus stimulation,[10] or epinephrine administration,[11] are similar. The present studies indicate that the vascular response in the patient with hypertension is essentially the same as in patients with normal blood pressure and normal kidneys. That these same changes in renal function are not altered by adrenergic blockade would seem to indicate renal autonomous adjustment to decreased systemic blood pressure, independent of autonomic regulation in this group of patients with hypertension. An alternative explanation would be that the kidney, like the heart,[12] is not subject to this adrenergic blocking agent or that it is less sensitive than other areas. A similar study in human beings, using autonomic ganglionic blockade with oral hexamethonium, shows similar results.[13]

The changes in urine sodium and potassium excretion rates in the tilted position did not vary significantly before or after adrenergic blockade, favoring further the possibility that the kidneys are less sensitive to adrenergic blockade than are other areas. Here again, the response in this group of patients with and without renal damage is no different from that which has been observed in normal persons. The depression of water excretion which is greater than the depression in glomerular filtration rate suggests that the liberation of antidiuretic principle may play a role in the increased tubular reabsorption of water. An elevation of the hematocrit indicating hemoconcentration would have given added credence to this, but we did not observe such an effect. This does not obviate the possibility of intracranial hemoconcentration in the caudally tilted position. Should this explanation be accepted one could not explain the increase in tubular reabsorption of sodium since it has been shown that the antidiuretic hormone does not increase sodium reabsorption in man.[14] Therefore, we must conclude that the antidiuretic effect of tilt is primarily a response to vascular and neurogenic influences which have not been blocked with Dibenzyline. The presence of renal impairment as measured by glomerular filtration rate does not alter these responses. Thus, a kidney may have marked obliteration of vasculature and functional units, yet those units that remain respond to stress in the same fashion as do normal nephrons.

SUMMARY

1. Dibenzyline has been used orally in twelve hypertensive patients with and without renal disease to induce adrenergic blockade. The effects on renal hemodynamics were observed in both the recumbent as well as tilted positions.

2. In the recumbent position, adrenergic blockade produced a reduction in blood pressure without alteration in renal function. In the tilted position, the reduction in renal function was the same before and after adrenergic blockade, although the reduction in blood pressure was greater after adrenergic blockade. These changes were not related to the degree of renal impairment as measured by glomerular filtration rate.

3. These results suggest renal autonomous adjustment to decreased filtration pressure, independent of autonomic control or else a specific resistance of the kidney to adrenergic blockade.

4. The excretion of water and electrolytes in patients with hypertension and associated renal damage is depressed out of proportion to renal blood flow and glomerular filtration rate. This indicates that the effect of tilt on electrolyte excretion in the hypertensive patient is qualitatively similar to the normotensive subject without renal damage and is not affected by adrenergic blockade with Dibenzyline.

REFERENCES

1. Miller, S., Moyer, J., and Ford, R.: Clinical Results of Dibenzyline in the Treatment of Hypertension, New Eng. J. Med. (To be published.)
2. Haimovici, H., Moser, M., and Krakauer, H.: Effect of Oral 688A on Blood Pressure in Normotensive and Hypertensive Subjects, Proc. Soc. Exper. Biol. & Med. **77**:477, 1951.
3. Moser, M., Walters, M., Mastin, A. M., Taymor, R. C., and Metraux, J.: Chemical Blockade of the Sympathetic Nervous System in Essential Hypertension, Arch. Int. Med. **89**:708, 1952.
4. Moyer, J., and Handley, C.: Renal Hemodynamic and Blood Pressure Response to N-Phenoxyisopropyl-N-Benzyl-B-Chlorethylamine (SKF-688A), J. Pharmacol. & Exper. Therap. **104**:329, 1952.
5. Moyer, J. H., and Mills, L. C.: Hexamethonium—Its Effect on Glomerular Filtration Rate, Maximal Tubular Function, and Renal Excretion of Electrolytes, J. Clin. Investigation **32**:172, 1953.
6. Bradley, S. E., and others: Renal Function in Renal Disease, Am. J. Med. **9**:766, 1950.
7. Mills, L. C., Ford, R. V., and Moyer, J. H.: Unpublished data.
8. Selkurt, E. E., Hall, P. W., and Spencer, M. P.: Influence of Graded Arterial Pressure Decrement on Renal Clearance of Creatinine, P-Aminohippurate, and Sodium, Am. J. Physiol. **159**:369, 1949.
9. Moyer, J. H., and Handley, C. A.: The Problem of Renal Vascular Shunts, Am. J. Physiol. **165**:548, 1951.
10. Forster, R. P., and Maes, J. P.: Effect of Experimental Neurogenic Hypertension on Renal Blood Flow and Glomerular Filtration Rates in Intact Denervated Kidneys of Unanesthetized Rabbits With Adrenal Glands Demedullated, Am. J. Physiol. **150**:534, 1947.
11. Moyer, J. H., and Handley, C. A.: Norepinephrine and Epinephrine Effect on Renal Hemodynamics, Circulation **5**:91, 1952.
12. Nickerson, M.: The Pharmacology of Adrenergic Blockade, J. Pharmacol. & Exper. Therap. **95**:27, 1949.
13. Ford, R. V., Moyer, J. H., and Spurr, C. L.: Hexamethonium in the Chronic Treatment of Hypertension—Its Effect on Renal Hemodynamics and Excretion of Water and Electrolytes (To be published).
14. Murphy, R., and Stead, E. A.: Effects of Exogenous and Endogenous Posterior Pituitary Antidiuretic Hormone on Water and Electrolyte Excretion, J. Clin. Investigation **30**:1055, 1951.

STUDIES WITH INTRAVENOUS GITALIN

II. Ballistocardiographic and Electrokymographic Observations

Olga M. Haring, M.D.,* and Aldo A. Luisada, M.D.**

Chicago, Ill.

THE clinical effects of gitalin, a digitalis glycoside, as well as the electrocardiographic changes produced by its intravenous administration, were discussed in a previous note.[1] Comparisons of the rapidity of action, rate of elimination, and therapeutic ratio between gitalin and other digitalis glycosides were also made. It was proved that the therapeutic ratio of this drug is higher than that of other digitalis glycosides.

A more complete evaluation of the action of gitalin requires demonstration that, while the therapeutic ratio is different, the changes of cardiovascular dynamics are similar to those caused by other, better known, glycosides.

The glycosides used in this study were administered in the following doses: (a) gitalin (Gitaligin),† 2.5 to 4 mg.; (b) strophanthin K (Strophosid),‡ 0.25 mg.; (c) lanatoside C (Cedilanid),‡ 0.40 mg.; (d) digitoxin (Crystodigin),§ 0.20 mg. Whenever more than one glycoside was injected into the same patient, a suitable interval elapsed between one injection and the next. Usually, glycosides having a faster elimination (strophanthin, gitalin) were injected first; not less than three days elapsed before lanatoside C was injected; not less than five days before digitoxin was injected.

The changes of cardiac dynamics were studied in two ways: (a) directly, by means of electrokymograms of the left ventricular border; and (b) indirectly, by means of ballistocardiograms. Electrokymograms and ballistocardiograms were recorded before and after intravenous injections of the digitalis glycoside. Electrocardiograms were recorded systematically and completed the study.[1]

From the Division of Cardiology of The Chicago Medical School and the Mt. Sinai Hospital of Chicago.

This study was performed under the tenure of a teaching grant of the National Heart Institute, United States Public Health Service, held by Dr. Luisada. It was made possible by a two-year grant of the White Laboratories, Inc., of Kenilworth, N. J., and by a grant of the Chicago Heart Association.

Received for publication March 12, 1953.

*Research Associate, Div. of Cardiology; Assistant of Medicine, The Chicago Medical School.

**Associate Professor of Medicine and Director, Division of Cardiology, The Chicago Medical School.

†Supplied by White Laboratories, Inc.

‡Supplied by Sandoz Pharmaceuticals.

§Supplied by Eli Lilly and Company.

MATERIAL AND METHODS

Eleven persons were studied by means of electrokymography, fourteen by ballistocardiography. Five persons were studied by both methods.

The electrokymograms were recorded in three normal persons, one patient with rheumatic heart disease, and seven patients with coronary heart disease; two of the latter had a history of previous myocardial infarction; one also had hypertension, another had atrial fibrillation. The age of the subjects ranged from 13 to 72 years. All patients presented some evidence of congestive failure. None of them had received digitalis within the last month.

The ballistocardiograms were recorded in three normal persons, one patient with rheumatic heart disease and ten patients with coronary heart disease. Four of the latter had a history of previous myocardial infarction; two also had hyertension; and two had atrial fibrillation.

Electrokymograms.—The electrokymograms were recorded by means of a Sanborn electrokymograph and either a poly-viso direct writer or a twin-beam photographic recorder. The patient was placed in a sitting position. The technique followed has been described by one of us;[2] the slit of the phototube was placed at about half-way of the left ventricular contour, in order to minimize the causes of error due to ventricular motion and to record mostly volume changes. A tracing was recorded before the injection. The cardiac glycoside was injected then into a vein of the forearm without moving the patient. The tracing was repeated soon after the injection and again within 20 minutes. The patient was allowed then to rest on a couch, but another tracing was recorded one hour after the injection. In one case, a further tracing was recorded after 2 hours. Special care was taken to place the slit in exactly the same position as before the injection. The controls of the electrocardiograph and electrokymograph were never adjusted after the initial setting in order not to alter the degree of amplification.

The ventricular electrokymogram was recorded at various film speeds: first, 75 mm./sec. in the photographic records or 50 mm./sec. in the direct writing, then, 2.5 mm./sec. in either or both of them. Thus, it was possible to analyze in detail the tracing (high speed) and to grasp quickly the maximal amplitude of the ventricular wave (low speed).

The tracings were recorded during voluntary apnea in an intermediate position between inspiration and expiration. This required instruction and a few experiments before beginning the study.

Among the clinical cases, one patient received on different days, gitalin, digitoxin, and strophanthin; one received gitalin, lanatoside C, and strophanthin; two received gitalin and strophanthin; one, gitalin and lanatoside C; and one, gitalin and digitoxin. Thus, a comparative study of the effects of the various glycosides was possible.

Ballistocardiograms.—The ballistocardiograms were recorded by means of a Sanborn optical ballistocardiograph connected to either a poly-viso (direct writer) or a twin-beam (photographic recorder). The records were calibrated by releasing a spring which had been pushed against the vertex and which exerted

a pressure of 600 grams; the obtained deflection of the tracing was 2 cm. The subject was lying supine on a firm table. The records were taken before the injection, soon afterwards, and after about one hour. The tracings were recorded at two different speeds: first, a higher speed (75, 50, or 25 mm./sec.) for the study of the various waves; then, a speed of 2.5 mm./sec. for a better grasp of the over-all amplitude of the IJK complex. The tracings were recorded without filter, with the subject either in voluntary apnea or breathing normally.

Among the clinical cases, three patients received gitalin, lanatoside C, and strophanthin; one received gitalin, digitoxin, and strophanthin; one received gitalin and lanatoside C; and one, gitalin and strophanthin. Thus, the actions of various glycosides were compared in the same subjects.

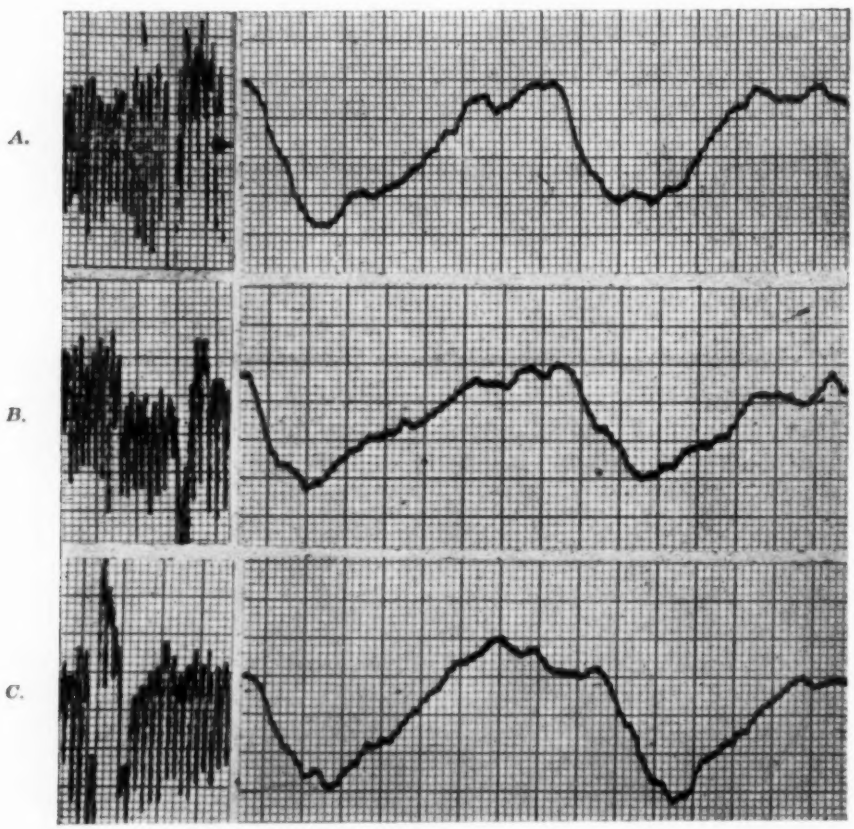

Fig. 1.—Electrokymogram of left ventricular border of a normal student. *A*, before injection; *B*, soon after intravenous injection of 4 mg. of gitalin; *C*, one hour after the injection; reduced amplitude in *B*; control values in *C*.

RESULTS

I.—Electrokymograms (Table I)

A. Normal persons:—Soon after the injection, there was a decrease of the heart rate in one person, a 10 per cent increase in the other two. The electrokymogram presented a 10 to 15 per cent decrease in all three subjects. Correlation of the change of electrokymographic amplitude with that of rate indicates

TABLE I. CHANGES OF THE ELECTROKYMOGRAM

TABLE I. CHANGES OF THE ELECTROKYMOGRAM

NO.	NAME	AGE	SEX	CLINICAL DIAGNOSIS	CHANGES SOON AFTER INJECTION		CHANGES 1 HOUR AFTER INJECTION		DRUG USED	TOTAL DOSE (MG.)	NO. OF INJEC.
					RATE (%)	EKG (%)	RATE (%)	EKG (%)			
1	F. C.	23	M	Normal	−10	−15	Control values	Control values	Gitalin	4	1
2	F. S.	23	M	Normal	+10	−10	Control values	Control values	Gitalin	4	1
3	A. J.	22	M	Normal	+10	−10	−10	+10	Gitalin	2.5	1
4	D. M.	13	F	R.F. R.H.D.	+10	+20	Control values	Control values	Gitalin Digitoxin	4 0.2	2
5	F. E.	50	F	C.H.D.	None	−30	−10	−20	Gitalin Digitoxin Strophosid	4 0.2 0.25	3
6	L. A.	70	M	C.H.D. Auric. fibr.	None	None	+10	+15	Gitalin Strophosid	3 0.25	2
7	McG. E.	58	M	C.H.D. Myoc. inf.	None	+10	None	−20	Gitalin	3	1
8	T. J.	70	M	C.H.D. Myoc. inf.	−10	−10	Control values	Control values	Gitalin	3	1
9	N. W.	72	M	C.H.D.	−20	−10	−20	Control values	Gitalin Lanatoside C. Strophosid	6 0.4 0.25	3
10	H. S.	61	F	H.C.H.D.	None	−20	None	Control values	Gitalin Lanatoside C.	12 0.4	5
11	D. L.	72	F	C.H.D.	None	−20	−10	−25	Gitalin Strophosid	2.5 0.25	2

The larger doses of gitalin indicated in this table and in Table II correspond to a solution which had lost part of its activity because of chemical action of the container. Correct values should not exceed 4 mg. of active glycoside.

R.F. = rheumatic fever ; R.H.D. = rheumatic heart disease; C.H.D. = coronary heart disease; H.C.H.D. = hypertensive cardiovascular heart disease.

an actual decrease in only one case (Case 1), because tachycardia may explain a proportional decrease in amplitude of contraction in the other two (Cases 2 and 3).

One hour after the injection, only Case 3 presented changes. These, however, were not significant because cardiac rate and amplitude of contraction varied 10 per cent in the opposite direction, so that the changes may be considered related to each other.

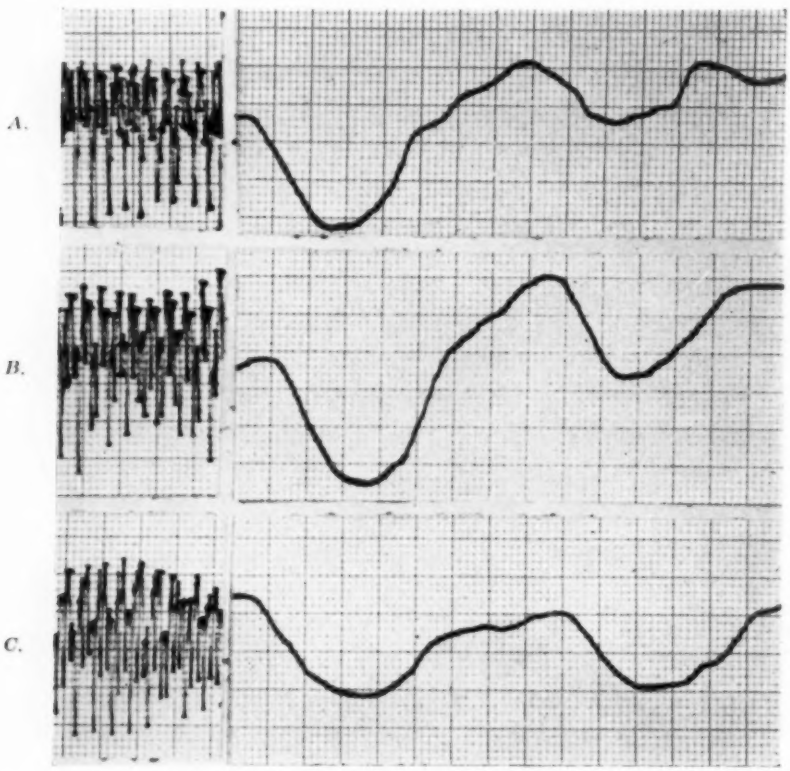

Fig. 2.—Electrokymogram of left ventricular border of a patient with coronary heart disease and atrial fibrillation. *A*, before injection; *B*, soon after intravenous injection of 0.24 strophanthin K; *C*, one hour after the injection; slight increase of amplitude and rate in *B*; slight average increase also in *C* (not well revealed by single contractions).

B. Clinical cases:—Soon after the injection, the heart rate was unchanged in five cases; it decreased from 10 to 20 per cent in two cases and increased 10 per cent in one. The amplitude of the ventricular electrokymogram was unchanged in one case; it increased 10 per cent in one; 20 per cent in another; and it decreased from 10 to 30 per cent in five cases. Correlation of the changes of rate with the electrokymographic changes indicates that a decrease in amplitude of contraction took place in five cases while there was a relative increase in two cases (Case 4 and 7), and no change in another (Case 6). The effects of lanatoside C, digitoxin, and strophanthin were similar when compared in the same patients.

One hour after the injection, the heart rate had decreased by from 10 to 20 per cent in three cases, had increased 10 per cent in one case, and had returned to control values in the others. The amplitude of the electrokymogram had decreased from 20 to 25 per cent in three cases; it had increased 15 per cent in one case (Case 6), and had returned to control values in the other four. Correlation of electrokymographic changes with changes of rate showed that there was a relative decrease in three cases; there was a relative increase in two cases (Cases 6 and 9); the others were practically unchanged. The effects of lanatoside C, digitoxin, or strophanthin were comparable in the same cases.

II.—Ballistocardiograms (Table II)

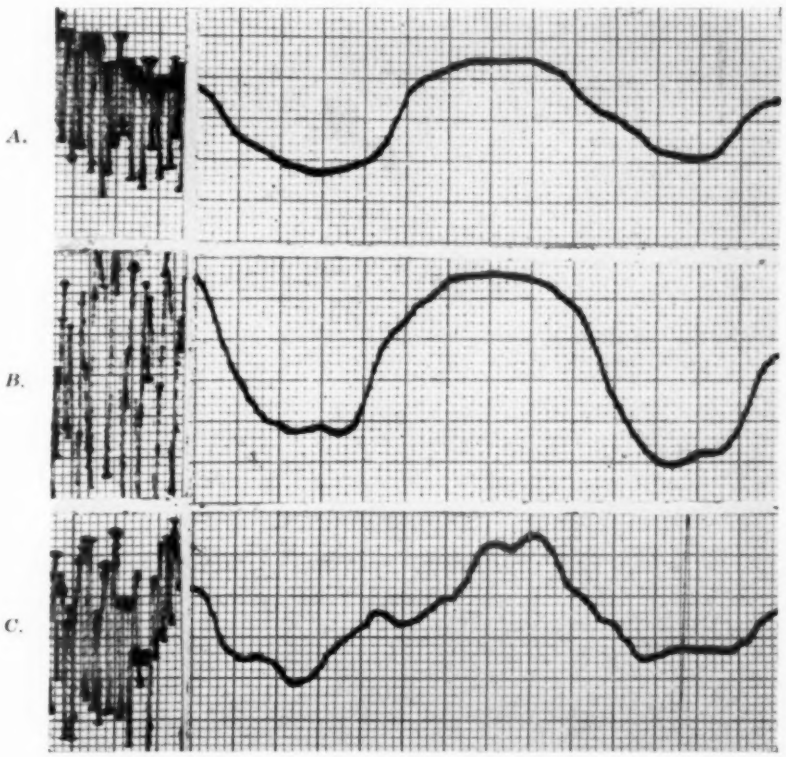

Fig. 3.—Electrokymogram of left ventricular border of same patient of previous figure; intravenous injection of 3 mg. of gitalin. Results are comparable to those of Fig. 2.

A. Normal persons:—Soon after the injection, no change of heart rate was present in any subject. On the other hand, the ballistocardiogram decreased from 10 to 25 per cent in two subjects, while the third could not be studied. A relative decrease of the ballistocardiogram was thus present in the two normal subjects which were studied.

One hour after the injection, no change of rate was present. The ballistocardiogram was decreased from 10 to 20 per cent in all cases. This represented also a relative decrease on account of the stability of the cardiac rate.

TABLE II. CHANGES OF THE BALLISTOCARDIOGRAM

NO.	NAME	AGE	SEX	CLINICAL DIAGNOSIS	CHANGES SOON AFTER INJECTION		CHANGES 1 HOUR AFTER INJECTION		ASPECT OF BCG	DRUGS	TOTAL DOSE (MG.)	NO. OF INJEC.
					RATE (%)	BCG (%)	RATE (%)	BCG (%)				
1	G. A.	24	M	Normal	None	−25	None	−10	Normal	Gitalin	4	1
2	B. N.	26	M	Normal	None	−10	None	−20	Normal	Gitalin	2.5	1
3	G. G.	27	M	Normal	None	—	None	−20	Normal	Gitalin	2.5	1
4	G. R.	33	F	R.H.D. M.I.S. A.I.S.	None	−50	−10	−60	Abnormal	Gitalin Lanatoside C.	11.5 0.8	9
5	M. H.	45	M	C.H.D. A.I.S. Myoc. Inf.	None	−25	−10	−25	Abnormal	Gitalin Lanatoside C. Strophanthin	11.5 0.8 0.5	10
6	S. R.	73	F	H.C.H.D.	−10	−20	Control values	−20	Abnormal	Gitalin	27	4
7	C. M.	62	M	C.H.D. Myoc. Inf.	None	−15	None	−15	Abnormal	Gitalin	6	2
8	F. E.	50	F	C.H.D.	None	−25	−10	−25	Abnormal	Gitalin Digitoxin Strophanthin	4 0.2 0.25	3
9	L. D.	70	M	C.H.D. Auric. Fibr.	None	None	+10	+10	Abnormal	Gitalin Strophanthin	3 0.25	2
10	McG. E.	58	M	C.H.D. Myoc. Inf.	None	—	None	−25	Abnormal	Gitalin	12	4
11	N. F.	72	F	H.C.H.D.	None	None	None	None	Abnormal	Gitalin	12	4
12	T. J.	70	M	C.H.D. Myoc. Inf.	−10	−15	Control values	Control values	Abnormal	Gitalin	3	1
13	N. W.	72	M	C.H.D.	−20	−20	−20	Control values	Abnormal	Gitalin Lanatoside C. Strophanthin	6 0.4 0.25	3
14	S. B.	71	F	C.H.D. Auric. Fibr.	−10	−20	−10	−20	Abnormal	Gitalin Lanatoside C. Strophanthin	6 0.4 0.25	9

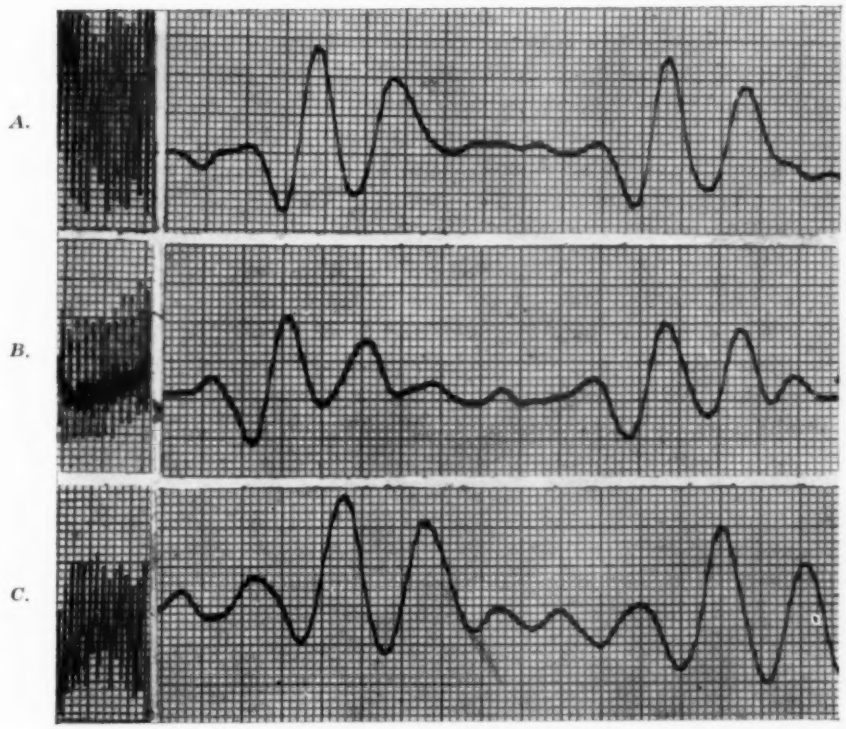

Fig. 4.—Optical ballistocardiogram of a normal student: *A*, before injection; *B*, soon after intravenous injection of 4 mg. of gitalin; *C*, one hour after injection; decreased amplitude in both *B* and *C* with relative increase between *B* and *C*.

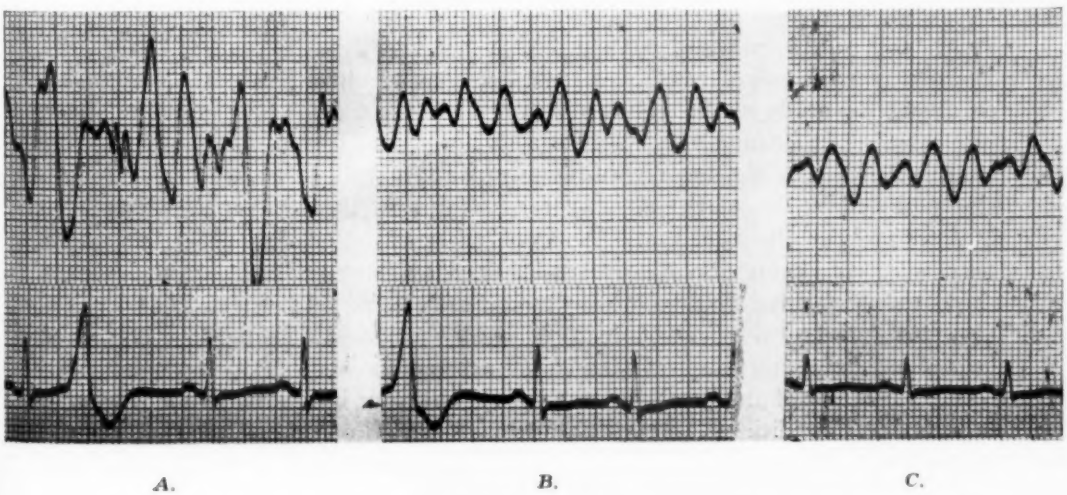

Fig. 5.—Optical ballistocardiogram and electrocardiogram in a case of rheumatic valvular disease: *A*, before injection; *B*, soon after intravenous injection of 3 mg. of gitalin; *C*, one hour after injection; greater regularity of the rhythm and decreased amplitude of the IJK complex in *B* and *C*.

B. Clinical cases:—Soon after the injection, the heart rate was found unchanged in seven cases; it was found decreased from 10 to 20 per cent, in four cases. The ballistocardiogram was unchanged in two; it was not recorded in one; it was decreased from 15 to 50 per cent in eight cases. Correlation of the ballistocardiogram with the cardiac rate revealed a relative decrease in eight cases out of eleven, and no change in two cases (the data of one case are not available). One hour later, the heart rate was still unchanged in three cases; it was decreased in five; it showed some increase in one case (Case 9); and it returned to control values in two cases. The ballistocardiogram showed no change in one case; a moderate increase in one case; a return to control values in two cases; and it presented a decrease of from 15 to 60 per cent in seven cases. Correlation of the changes of the ballistocardiogram with those of the heart rate showed a relative decrease in seven cases, no change in one, and a relative increase in three cases (Cases 6, 9, and 13).

DISCUSSION

The main purpose of this study was to ascertain whether or not gitalin has a cardiac and vascular action similar to that of other cardiac glycosides of the digitalis group. As the methods employed by us are different from those used by previous workers, certain deductions about the action of digitalis in general and the difference between digitalis and strophanthus glycosides may also prove of interest.

In the past, digitalis was studied clinically, in animal experiments, in heart-lung preparations, in isolated hearts, and in papillary muscle or myocardial strip preparations. Certain important deductions were obtained in normal persons or clinical patients by cardiac catheterization with pressure measurements within the right heart chambers and determination of cardiac output. Recently, a study of oral digitalization was made in normal persons;[3] cardiac output was determined by means of Ring's electrokymographic method while details of right and left ventricular pulses were also studied.

We used different techniques from those of previous workers. We considered that the study of the pulsations of the left ventricular border might give a direct proof of the functional changes of the left ventricle; on the other hand, the amplitude of the ballistocardiographic complex IJK, being related to the acceleration of blood in the aorta and with the strength of the left ventricle, gives an indirect proof of the same fact. We were aware of the possible objections which may be raised against direct correlations between the amplitude of the waves in the two tracings and mathematical data or even a certain property of the heart. However, the data were considered only in correlation with each other; no special importance was attached to the initial values, and the main interest was attached to the variations of amplitude of the waves in the same individual, under the same experimental conditions, and within a limited period of time. The fact that all drugs were pure glycosides and were injected intravenously added to the basic comparability of results.

A. General action of cardiac glycosides:—The most common early result of the injection was an absolute reduction in the amplitude of the pulsations of the

left ventricle and in the amplitude of the ballistocardiographic complex. Quite often this reduction coincided with a decrease in heart rate. On the other hand, a different behavior of the various patients was noted one hour after injection.

Correlation of the changes of the electrokymogram with those of the heart rate revealed an early decrease in one out of three normal persons and five out of eight clinical cases. On the other hand, one hour after injection, there was increase in two out of eight clinical cases, while a decrease was still present in three out of eight. No significant change was found in normal subjects one hour after injection.

Correlation of the changes of the ballistocardiographic complex showed a decrease in two out of three normal persons and in eight out of eleven clinical cases, a few minutes after the injection. A relative decrease was still found in three out of three normal persons and in seven out of eleven clinical cases, one hour after injection. On the other hand, three out of eleven clinical cases presented a relative increase one hour after injection.

Thus, early changes of both the electrokymographic and the ballistocardiographic amplitude consisted in a decrease. The changes of both of them after an hour were mostly in the sense of a decrease, while in about one-fourth of the cases they consisted of an increase.

There is a general agreement between various workers that digitalis has little action on the normal myocardium. However, such action was proved by Eddleman and co-workers.[3] Reduction of amplitude of the ballistocardiographic waves in our normal persons may be attributed to a decreased venous return on account of the peripheral effect of digitalis. The decreased amplitude of the left ventricular contractions may be explained in the same way; a decreased filling of the left ventricle would be followed by smaller contractions.

The action of digitalis in clinical cases is explained variously by different workers. McMichael and Sharpey-Schafer[4] admitted a chiefly peripheral effect while Cournand and co-workers[6] proved a direct effect on the myocardium. Further studies by McMichael[7] confirmed the conclusions of Cournand so that there now is agreement in admitting a double action of digitalis on the peripheral vessels and on the myocardium.

In considering the various actions of digitalis, one should always take into consideration: (a) the way of administration; (b) the glycoside; and (c) the time interval between administration and study of the patient. Usually, in experiments performed with cardiac catheterization, intravenous administration of the glycoside was used, and the observation was not prolonged beyond one hour. On the contrary, the study of Eddleman and co-workers was based on oral digitalization. It is reasonable to assume that the effects of oral digitalis in a normal person become apparent from 30 to 60 minutes later than those of intravenous digitalis.

In our experiments, the early decreased amplitude of pulsations of the left ventricle and the early decrease of the ballistocardiographic complex took place in a greater percentage of clinical cases than of normal persons. This decrease, which can be explained only by the result of a decreased venous return to the heart, points to a similarity of action of digitalis in normal persons and patients

in failure, even though it is more marked in the latter. On the other hand, observations made after one hour after the injection revealed that, in a significant percentage of clinical cases (about one-fourth), there was increase of the electrokymographic and ballistocardiographic waves in comparison with control values. It is likely that observations made several hours later would have remarkably increased this percentage.* The increase of the waves can be explained by stimulation of the digitalis glycosides on the myocardium.

Worthy of mention is the response of a 70-year-old patient (Case No. 6 in Table 1, No. 9 in Table 2) with coronary heart disease and auricular fibrillation. His average rate before injection of the glycosides was between sixty and seventy per minute. No change was noticeable immediately after injection. After about one hour, the rate had increased by 10 per cent while the amplitude of either the electrokymogram or the ballistocardiogram had also increased. This indicates a direct action of the drugs in stimulating the myocardium.

B. Effects of a single glycoside:—The old literature emphasized a difference of action between strophanthin (or ouabain) and digitalis. However, studies between 1910 and 1930 compared purely clinical observations made in different patients, treated either with intravenous ouabain or with oral digitalis. Therefore, comparison was difficult and subjective. More recently, different findings with ouabain and digitoxin by means of catheterization were explained by McMichael as indicating a somewhat different effect. However, even if the studies were performed in similar cases, no comparison was made in the same clinical cases. Our observations point to a basic similarity of effects between strophanthin, lanatoside C, and digitoxin; and between gitalin and the other glycosides. This indicates: (a) that the various strophanthus and digitalis glycosides have similar actions; (b) that gitalin acts in the same way as the other glycosides on the peripheral vessels and on the heart; and (c) that the clinical differences should be explained only by taking into consideration the dose, the way of introduction, the rate of elimination, and the therapeutic ratio of the various glycosides. It is possible that one or the other of the glycosides had a more rapid effect, but this was not detectable by our technique.

SUMMARY

An electrokymographic and ballistocardiographic study has been undertaken in order to study the effect of intravenous injections of various cardiac glycosides including strophanthin, gitalin, lanatoside C, and digitoxin. The electrokymogram of the left ventricular border or an optical ballistocardiogram were recorded before injection, soon after the injection, and about one hour later. Comparison was made between various glycosides in the same subjects. Eleven persons were studied by means of electrokymography, three normal persons and eight clinical patients. Fourteen persons were studied by means of ballistocardiography, three normal persons and eleven clinical patients. Five persons were studied by means of both methods. All clinical patients presented evidence of congestive failure.

*Jones[5] observed increase in amplitude of the ballistocardiographic waves 48 hours after oral administration. As the time interval is so much greater than that of our studies, his findings cannot be compared with ours.

Correlation of the changes in amplitude of left ventricular electrokymography with those of the heart rate revealed early decrease in one out of three normal persons and in five out of eight clinical patients. On the other hand, one hour after injection, there was an increase in two out of eight clinical patients while a decrease was still present in three out of eight. No significant change was found in normal persons one hour after injection.

Correlation of the changes of the ballistocardiographic complex IJK with those of the heart rate showed early decrease in two out of three normal persons, and in eight out of eleven clinical patients. One hour after injection, a relative decrease was found in three out of three normal persons, and in seven out of eleven clinical patients. Three out of eleven clinical patients presented a relative increase.

The early decreased amplitude of pulsations of the left ventricle took place in a greater percentage of clinical patients than of normal persons. This decrease can be explained by the result of a reduced venous return to the heart and points to a similarity of early action of digitalis glycosides in normal persons and in patients in failure. On the other hand, one hour after the injection, one-fourth of the clinical patients presented increase of the electrokymographic and ballistocardiographic waves. This can be explained by direct stimulation of the myocardium and was not present in normal persons.

No significant difference was found between the various cardiac glycosides in either the peripheral or the myocardial effect. This indicates that:

(1) Gitalin has a similar effect to that of other glycosides of the digitalis group; (2) clinical differences found by other workers and by the authors between the therapeutic ratio of gitalin and that of other glycosides are not due to basic difference in the mechanism of action.

REFERENCES

1. Haring, O. M., and Luisada, A. A.: Studies With Intravenous Gitalin. I. Clinical and Electrocardiographic Observations, Am. Heart J. **45**:108, 1953.
2. Luisada, A. A., Fleischner, F. G., and Rappaport, M. B.: Fluorocardiography. II. Observations on Normal Subjects, Am. Heart J. **35**:348, 1948.
3. Eddleman, E. E., Willis, K., Greve, M. J., and Heyer, H. E.: The Effect of Digitoxin on the Apparent Stroke Volume, Posteroanterior Cardiac Diameter, and the Cardiac Cycle in Normal Subjects as Studied by the Electrokymograph, Am. Heart J. **41**:161, 1951.
4. McMichael, J., and Sharpey-Schafer, E. P.: The Action of Intravenous Digitoxin in Man, Quart. J. Med. **13**:123, 1944.
5. Bloomfield, R. A., Rapoport, B., Milnor, J. P., Long, W. K., Mebane, J. G., and Ellis, L. B.: The Effects of the Cardiac Glycosides Upon the Dynamics of the Circulation in Congestive Heart Failure. I. Ouabain, J. Clin. Investigation **27**:588, 1948.
6. Harvey, R. M., Ferrer, M. I., Cathcart, R. T., Richards, D. W., Jr., and Cournand, A.: Some Effects of Digitoxin Upon the Heart and Circulation in Man. Digitoxin in Left Ventricular Failure, Am. J. Med. **7**:439, 1949.
7. Ahmed, S., Bayliss, R. I. S., Briscoe, W. A., and McMichael, J.: The Action of Ouabain (g-Strophanthin) on the Circulation in Man, and a Comparison With Digitoxin, Clin. Sci. **9**:1, 1950.
8. Jones, R. J.: The Nickerson Ballistocardiogram in Arteriosclerotic Heart Disease With and Without Congestive Failure, Circulation **6**:389, 1952.

A STUDY OF DIURETIC ACTION OF PAMABROM* (2-AMINO-2-METHYL-PROPANOL-1-8-BROMOTHEOPHYLLINE) IN CARDIAC FAILURE

JAMES E. DOHERTY, M.D., AND OWEN W. BEARD, M.D.

LITTLE ROCK, ARK.

THIS study was undertaken to determine if 2-amino-2-methyl-propanol-1-8-bromotheophylline (Pamabrom) would exhibit diuretic activity in patients with cardiac failure. Claims have been made that this preparation counteracts pituitary antidiuretic hormone activity, prevents the weight gain associated with water retention during the premenstrual phase of the menstrual cycle, and possesses low toxicity.

METHOD OF STUDY

Patients in severe cardiac failure, who had been followed in the cardiac clinic for at least three months, were selected for the study. In these patients, failure was poorly controlled on digitalis and ammonium chloride, and many of them required frequent injections of parenteral mercurial diuretics in order to maintain dry weight. There was no selection of patients according to age, sex, or etiologic diagnosis of heart disease. Patients who appeared to have progressive cardiac failure were excluded from the study. No changes were made in medication for each patient other than the addition of Pamabrom; thus, the period of observation prior to the study could be used as a control. Pamabrom was administered in divided doses of 300 to 900 mg. daily. The amount of mercurial diuretic injections required during therapy, together with gain or loss in weight, was closely followed. Other data such as presence of edema, degree of failure, subjective improvement, and the usual vital signs were recorded.

It is proposed that the effectiveness of the diuretic agent would be reflected by (1) differences in requirement of mercurial diuretics during the control and the study periods and (2) weight gain or loss during the period of study.

ANALYSIS OF DATA

Nineteen patients were included in this study. One failed to report for follow-up and, therefore, was lost. Of the eighteen remaining, (see Table I), four received Pamabrom only for 5 to 7 days. Case 1 developed gross hematuria and

TABLE I. ANALYSIS OF DATA ON PATIENTS RECEIVING PAMABROM

From the Division of Cardiology, Department of Medicine, University of Arkansas School of Medicine, Little Rock, Ark.

Received for publication March 13, 1953.

*Supplied by J. M. Holbert, Ph.D., Research Director, Chattanooga Medicine Company, Chattanooga, Tenn.

TABLE I. ANALYSIS OF DATA ON PATIENTS RECEIVING PAMABROM

CASE NO.	SEX RACE	AGE	DIAGNOSIS	DOSE DAILY (MG.)	DURATION OF THERAPY (DAYS)	TOXIC MANIFESTATIONS	WEIGHT CHANGE (LBS.)	MERCURIAL PER WEEK		COMMENT
								CONTROL (c.c.)	ON PAMABROM (c.c.)	
1	NF	61	HCVD	600	6	Gross hematuria 4+ albuminuria	+6	2	2	Poor response, admitted to hospital for study, see text
2	WM	55	HCVD	900	5	None	+3	4	4	Poor response
3	NM	66	HCVD	300	4	None	+4	None	None	Poor response
				900	3	None	+4	None	None	
4	NM	58	ASHD	600	7	None	+1	2	2	Poor response
				900	28	None	−1	1	1	
5	NM	70	PHD	600	22	Nausea and vomiting	−3	2	2	Poor response, received 2 c.c. mercurial in emergency room day before last weight was recorded
6	NF	44	HCVD	600	14	Nausea and vomiting	−9	2	2	Difficult to evaluate response because of nausea and vomiting, appears to be fair response
7	NF	49	HCVD	600	30	Acute pyelonephritis	−3	2	1/8	Good response
8	NM	79	SHD	600	9	None	−3½	4	4	Fair response
			ASHD	900	10	None	+½	4	4	
9	WM	78	ASHD	600	7	None	+8	1	0	Poor response
10	WM	64	ASHD	600	20	4+ nausea	−3	1	1	Fair response
11	NM	65	ASHD	600	24	Maculopapular rash	−3	None	None	Fair response, rash cleared when therapy discontinued
12	NF	46	HCVD	600	14	None	−½	1	1	Poor response
				900	53	None	+4	1	3	
13	NM	50	Prob.	600	9	None	−9	None	None	Good response
			ASHD	900	4		+1	None	None	Fair response—not at dry weight
14	NM	60	ASHD	600	67	None	+15½	2	1	Poor response, paracentesis—3 liters fluid accounts for weight loss
				900	70	Diarrhea	−3	2	1	
15	NF	62	ASHD	600	21	None	+2	2½	4	Poor response
16	NF	71	ASHD	600	7	None	+6	1	2	Poor response, patient still marked failure
				900	29	None	−4	1	2	
17	NF	51	RHD	600	21	Nausea and vomiting	−½	1	1	Poor response
18	NM	70	ASHD	600	35	None	+5	½	½	Poor response, additional mercurial invalidates weight loss
				900	35	None	−5	½	1	

N = Negro; W = white; HCVD = hypertensive cardiovascular disease; ASHD = arteriosclerotic heart disease; PHD = pulmonary heart disease; SHD = syphilitic heart disease; RHD = rheumatic heart disease.

gained six pounds in weight while receiving 600 mg. of Pamabrom daily for six days and mercurial diuretics at the same dosage as during the control period. Pamabrom was discontinued, and the patient was admitted to the hospital where extensive study failed to reveal any cause for the hematuria. The hematuria subsided during the period of hospitalization, and there has been no recurrence. Further trial on Pamabrom was not attempted. The remaining three patients (Cases 2, 3, 9), who received short term trials, exhibited such a sudden weight gain over the short period of observation, it was felt that treatment should be discontinued.

Fourteen patients received the preparation from 14 to 137 days. Four patients (Cases 5, 6, 10, 17) developed nausea or vomiting severe enough to warrant discontinuing medication. Case 14 developed a mild diarrhea after 120 days of treatment. Originally, Pamabrom was not thought to be responsible, but since the diarrhea continued for 17 days while the patient was still receiving Pamabrom and promptly subsided when the drug was discontinued, we believe that this represented a toxic reaction.

During the fourth week of therapy, Case 11 developed a maculopapular rash, which cleared after the drug was discontinued.

During the fifth week of treatment Case 7 developed acute pyelonephritis which was probably unrelated to the drug, otherwise diuretic response in this patient was good. In the remaining seven patients the drug was well tolerated, and with the exception of Case 13, they failed to exhibit significant change in weight or decreased requirement of mercurial diuretic.

SUMMARY

1. Eighteen cases of chronic congestive heart failure were given Pamabrom as a diuretic agent. One patient was lost in the follow-up, and four received only a short term trial.

2. Medication was discontinued in four cases because of nausea and vomiting; in one, because of diarrhea; in one, because of skin rash; in one, because of gross hematuria (possibly unrelated).

3. Two patients of the eighteen studied exhibited good diuretic response. Medication was discontinued in one because of acute pyelonephritis, probably unrelated to the drug.

4. In the remaining six patients, significant diuresis, manifested by weight loss or maintenance of weight with a reduction in requirement of mercurial diuretic, was not observed.

CONCLUSION

Pamabrom* (2-amino-2-methyl-propanol-1-8-bromotheophylline) appears to have little value in the treatment of patients in chronic congestive heart failure in the dosage administered.

*New Drug Application Number 8451, Brayten Pharmaceutical Company, (Chattanooga Medicine Company) Chattanooga, Tenn.

VASCULAR CHANGES IN HYDRONEPHROSIS

RUDOLF ALTSCHUL, M.U.Dr., AND SERGEY FEDOR, B.A.

SASKATOON, SASK.

IN EXPERIMENTAL as well as in spontaneous hydronephrosis the interlobar arteries are overstretched on account of the increased distance between their point of origin in the sinus and the thinned-out cortex. In the later stage, when the organ is reduced in size because of reabsorption, the interlobar arteries may become tortuous (Egger[2]). The arciform and cortical arteries, however, have already become tortuous in the first stage of hydronephrosis. The cause of the convoluting of peripheral branches is not definitely established. Several factors have to be considered: (a) there is an intense parenchymal atrophy and the vessels become, as it were, too long for the thin layer of parenchyma; (b) extravascular pressure is increased and interferes with circulation in the arteries and, still more, in the veins. This condition may combine (c) with the obliteration of glomerular and other capillaries. The obliteration is readily understood as being caused by pressure which is due to the accumulation of fluid in the hydronephrotic sac, but it may, at least partly, be due to an intrinsic factor, since the atrophic organ needs a lesser blood supply than the normal kidney. The obliteration of a great part of the capillary network (c) and compression of the thin-walled veins (b) will slow down circulation with, at least, a temporary damming up of blood in the arteries. Whether a proximal increase in blood pressure is responsible for the contorting of arteries is doubtful in view of the observation that in the proximal segments of ligated vessels a hypertension is not found. Nevertheless, the damming may be the main or a contributory cause of the tortuosity.

While studying microscopic sections of kidneys, the ureter of which had been ligated to set the organ out of action for a different purpose, it was found that many vessels had severe tears in their elastica interna together with some endothelial proliferation. This observation was followed up by the ligation of ureters in a greater number of experimental animals and by studying human hydronephrosis, with the object of gaining more insight into this vascular change. We have found no reference in the literature concerning reactions of the elastica and endothelium in the vessels of hydronephrosis and therefore report them here.

From the Department of Anatomy, University of Saskatchewan.

This is part of a work supported by a grant from the Life Insurance Medical Research Fund.

Received for publication March 20, 1953.

MATERIALS AND METHODS

Ureters were ligated unilaterally in eight rabbits and in ten white rats. The animals were allowed to survive from 7 to 187 days. They were killed by intravenous air injection or chloroform. The kidneys were fixed in situ with formaldehyde solution for twenty-four to forty-eight hours and then carefully removed. After embedding and sectioning, the tissues were stained with hematoxylin-eosin and by Unna-Tänzer's or Verhoeff's elastica methods. In several cases, serial sections were made, in order to follow up the lesions in the elastica interna. Human specimens were obtained from the Department of Pathology,* University of Saskatchewan.

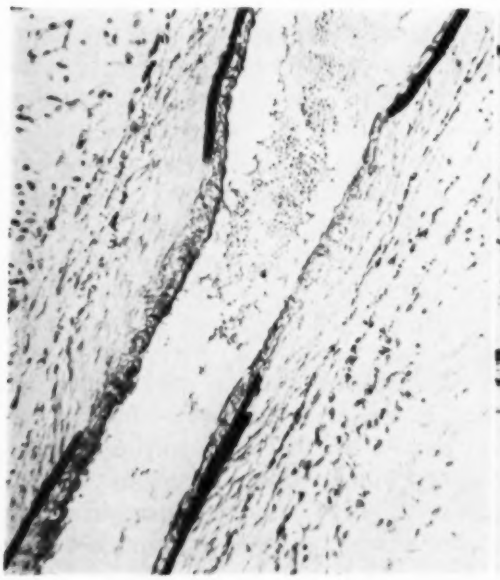

Fig. 1.

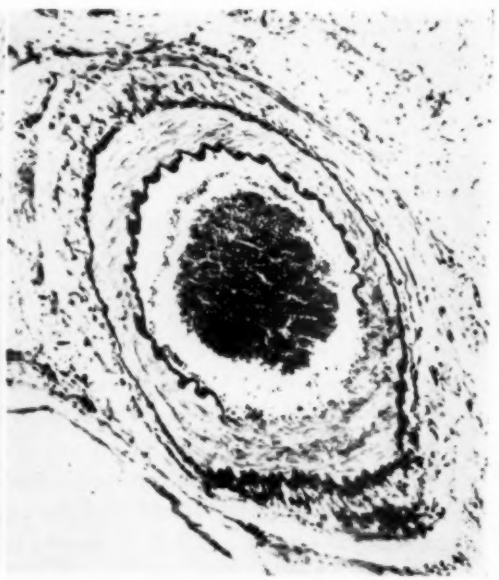

Fig. 2.

Fig. 1.—Rabbit. Interlobar branch of renal artery, 44 days after ligation of a ureter. Verhoeff's elastica stain. × 180. Reduced ⅓ for journal reproduction.

Fig. 2.—White rat. Interlobar branch of renal artery, 124 days after ligation of a ureter. Verhoeff's elastica stain. × 96. Reduced ⅓ for journal reproduction.

RESULTS AND DISCUSSION

As early as seven days after the onset of experimental hydonephrosis, kidney sections, stained for elastic tissue, show numerous tears in the elastica interna of large and small branches of the renal artery. Artifacts can be definitely ruled out. The tears occur in either a longitudinal or in a transverse direction, that is, the torn margins are seen separated in a longitudinal (Fig. 1) or in a transverse direction (Fig. 2). In later stages, the elastica interna will show elastosis, that is, splitting into numerous lamellae with the addition of new elastic layers (Fig. 3).

Splitting into lamellae and proliferation of the elastica interna have been reported in otherwise normal vessels in man in early life (Hackel[4]), especially near

*Courtesy of Dr. D. F. Moore.

orifices or branchings and, also, in the course of arteriosclerosis, but primary tearing is mentioned less frequently or not at all (Lewin[3]). Lamellation and proliferation of the elastica interna are readily observed, also, in ligated arteries, where tears are also found (Schaeffer and Radasch,[5] and many others) although they are less frequent and of lesser extent than in hydronephrosis.

The pathologic changes in ligated arteries differ from those in hydronephrosis in that, in the latter, the tearing appears to be the primary and principal change, while in ligated arteries the splitting into lamellae and neoformation of elastica are more conspicuous. In arteries of hydronephrosis, the torn elastica seems to recoil more than in ligated vessels, or in arteriosclerosis. Figure 4 shows such a recoiling and Fig. 5 a thickening which, most likely, is due to a contraction of the elastic membrane. This contraction brings to one's mind the expression "vital rubber" or "animal rubber," both of which terms have been used to describe the rubberlike quality of elastic tissue (H. J. Wells[7]; F. H. Wykoff[8]).

Although the stretching of the larger interlobar arteries is different from the contorting of cortical vessels, both entail an elongation with a consequent tearing of the elastica.

In hydronephrosis, the endothelium in vessels with tears in the elastica proliferates to a very slight degree in rats but to a somewhat higher degree in rabbits (Figs. 1 and 6). If compared, however, to the endothelial reaction in ligated arteries of either rats or rabbits, the endothelial reaction in hydronephrosis is of much slower onset, even in rabbits, and does not reach the same intensity. Thus, we find in ligated vessels a stronger elastosis and a stronger endothelial reaction, which may well be related to each other.

The endothelial proliferation in ligated vessels has been explained as being due to the lack of oxygen (Schaeffer and Radasch[5]; Altschul[1]). Similarly, in hydronephrosis of the rabbit, an oxygen deficiency, although of a lesser degree, may exist. In contrast to ligated vessels, hydronephrosis will have, at least for some time after the onset of the collection of fluid in the occluded kidney, a minimal blood circulation, which will be sufficient for the needs of the vessel wall. Only when the circulation diminishes further because of increasing extravascular pressure and of obliteration of capillaries, will the vessel wall suffer a more severe hypoxemia, with subsequent proliferation of the endothelial cells. On the other hand, the endothelial proliferation in ligated vessels may represent a reparative process of the vessel wall, the wall having been weakened by the rupturing of the elastica. This view has been advocated by Ssolowjew.[6]

Regarding the difference between the endothelial reaction in hydronephrosis in rabbits and in rats, it is worth pointing out that in rats, in contrast to rabbits, experimental cholesterol arteriosclerosis cannot be elicited, unless special, additional factors have been introduced. Therefore, it seems logical to accept the different endothelial reaction in hydronephrosis as supporting evidence for the view that differences in the reaction of endothelium are responsible for the resistance in the rat, or lack of resistance in the rabbit, towards cholesterol arteriosclerosis.

It is interesting to examine also the elastica interna in hydronephrosis of man. In the great majority of cases, however, the damage already will have lasted

Fig. 3.

Fig. 4.

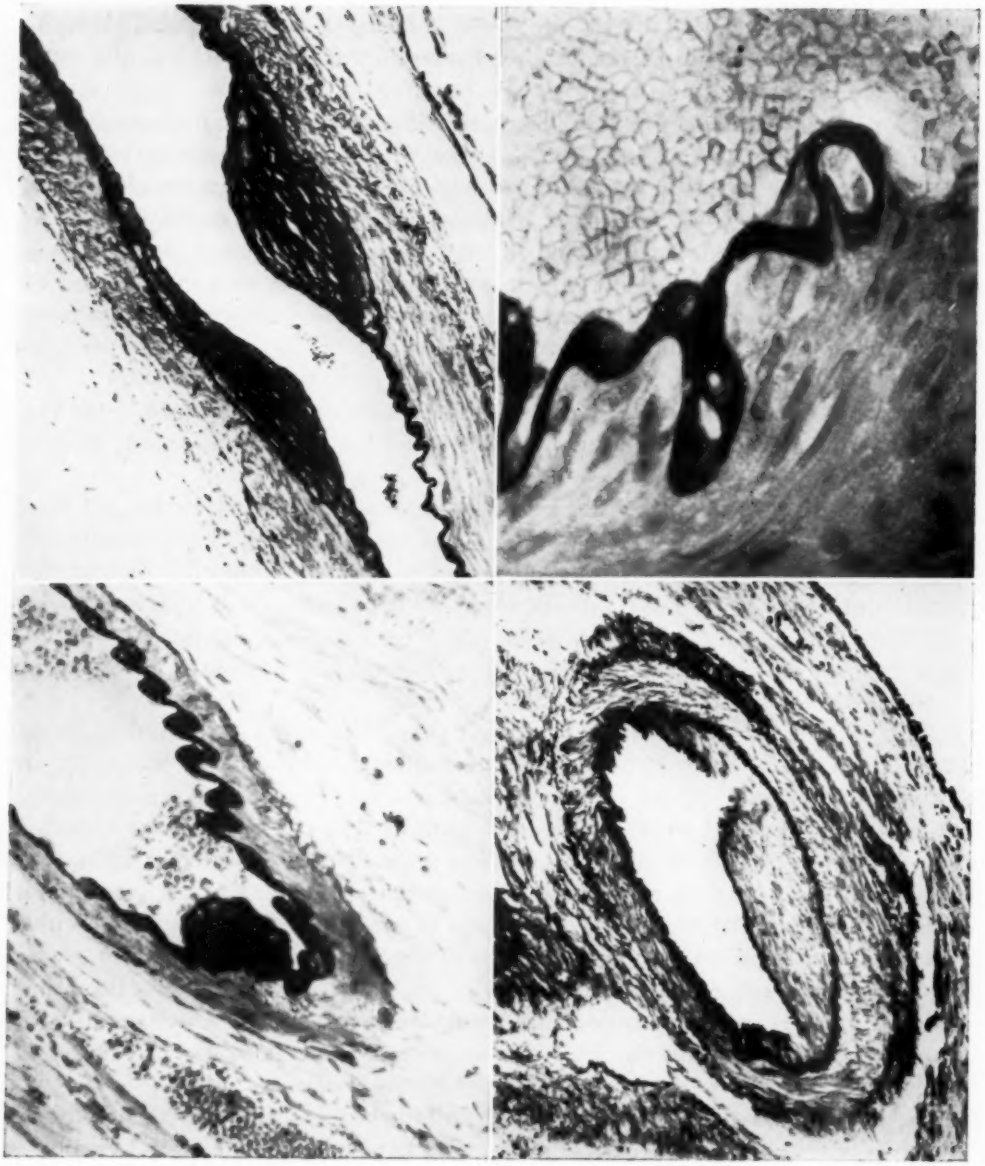

Fig. 5.

Fig. 6.

Fig 3.—Rabbit. Interlobar branch of renal artery, 116 days after ligation of a ureter. Verhoeff's elastica stain. × 200. Reduced ⅓ for journal reproduction.

Fig. 4.—White rat. Cortical branch of renal artery, 110 days after ligation of a ureter. Verhoeff's elastica stain. × 880. Reduced ⅓ for journal reproduction.

Fig. 5.—White rat. Interlobar branch of renal artery, 172 days after ligation of a ureter. Verhoeff's elastica stain. × 300. Reduced ⅓ for journal reproduction.

Fig. 6.—Rabbit. Interlobar branch of renal artery, 96 days after ligation of a ureter. Verhoeff's elastica stain. × 200. Reduced ⅓ for journal reproduction.

for a relatively long time before it is possible to secure a specimen for microscopic examination, and thus the important first stages in the elastica damage are lost for observation. Moreover, since the lesion will occur mainly in adult persons, a differentiation from arteriosclerotic changes becomes very difficult. In the human material of hydronephrosis which was at our disposal, we found a great deal of splitting in the elastica accompanied by little degenerative phenomena, but since the tearing proper was not obvious it is very likely that repair processes have "breached the gap."

SUMMARY

In experimental hydronephrosis of rabbits and rats, the cortical vessels become contorted, and the interlobar arteries overstretched. In both sets of vessels the elastica interna is torn, which tearing may be followed by elastosis. In comparison to elastosis seen in ligated vessels, that in hydronephrosis is rather scanty. Endothelial proliferation in vessels with torn elastica appears later in hydronephrosis than in ligated vessels. It is much less in rats than in rabbits. This species difference in endothelial reaction has perhaps a relation to the difference in susceptibility of the two species for cholesterol arteriosclerosis.

REFERENCES

1. Altschul, R.: Selected Studies on Arteriosclerosis, Springfield, Ill., 1950, Charles C Thomas.
2. Egger, K.: Die Veraenderungen des Nierenarteriensystems in der Hydronephrose, Ztschr. f. urol. Chir. u. Gynäk. **44:**138, 1938.
3. Lewin, J.: Ueber die Ausbreitung der sogenannten Querstreifen, Virchows Arch. f. path. Anat. **295:**39, 1935.
4. Hackel, W. M.: Ueber den Bau und die Altersveraenderungen der Gehirnaterien, Virchows Arch. f. path. Anat. **266:**630, 1927.
5. Schaeffer, J. Parsons, and Radasch, H. E.: On the Obliteration of the Lumen of Blood Vessels, Am. J. Anat. **33:**219, 1924.
6. Ssolowjew, A.: Ueber experimentell hervorgerufene Elasticarisse der Arterien, Virchows Arch. f. path. Anat. **283:**213, 1932.
7. Wells, H. J., in Cowdry, E. V.: Arteriosclerosis, New York, 1933, The Macmillan Company.
8. Wykoff, F. H., *in* Cowdry, E. V.: Arteriosclerosis, New York, 1933, The Macmillan Company.

PERSISTENT TRUNCUS ARTERIOSUS

Report of Two Cases With Right Aortic Arch

Richard D. Rowe, M.B.(N.Z.), M.R.C.P.(E), and Peter Vlad, M.D.

Toronto, Ont.

TRUNCUS arteriosus is an interesting but rare congenital malformation of the heart usually resulting in death in very early life. For years, the majority of accounts of the condition have concerned themselves chiefly with descriptions of the morbid anatomy. There has been considerable confusion over what constitutes true truncus arteriosus, but recently an excellent review by Collett and Edwards[1] has clarified the anatomic situation.

From the clinical viewpoint Taussig[2] was the first to describe in detail a technique using fluoroscopy whereby ante-mortem diagnosis of this anomaly, especially in newborn infants, was made possible.

Angiocardiography would theoretically offer more certain confirmation of the diagnosis in suspected cases but so far no proved instances have been reported.[3] There is also a conspicuous absence in the literature to date of complete electrocardiograms in this malformation.

The present report concerns two infants with autopsy-proved truncus arteriosus and right aortic arch in whom the pulmonary arteries arose directly from the single vessel. Both patients had electrocardiographic studies, and one underwent venous angiocardiography in addition.

CASE REPORTS

Case 1. T. B., a white boy, was born at term after a normal pregnancy, May 30, 1952. Delivery was spontaneous. The birth weight was 7 pounds 4 ounces. The family history was noncontributory. He was breast fed for four days but nursed poorly. On the fourth day he was found to be a grey-blue color and breathing rapidly. Twenty-four hours after the onset of these symptoms he was transferred from a maternity hospital with the provisional diagnosis of atelectasis.

On admission to the Hospital for Sick Children he had moderate dyspnea and slight generalized cyanosis which seemed to lessen from the lips on crying. The thoracic cage was normal but air entry was diminished and percussion impaired over the left chest. The apex beat was 160 per minute and was palpable in the fourth left intercostal space at the anterior axillary line. A grade 3 blowing systolic murmur was audible maximally at the fourth left intercostal space near the apex and radiated to the axilla and back. No thrill was palpable. Triple rhythm was present. Both femoral arteries were easily palpable. The liver was not enlarged. Roentgenograms of the chest in the anteroposterior view (Fig. 1) showed a displaced heart occupying the

From the Hospital for Sick Children, Toronto, Ont., and Department of Pediatrics, University of Toronto, Toronto, Ont.

Received for publication March 27, 1953.

left chest. The contour was obscured by a uniform opacity of the whole left hemithorax. The intercostal spaces on the left were crowded. The hilar shadows visible only on the right were slightly increased. In the left oblique view (Fig. 2) the right ventricle was enlarged and projected forward. A large aorta indented the esophagus.

The following day slight cyanosis was present only when out of oxygen and dyspnea was less evident. Triple rhythm was not detected. An oximetric examination revealed an arterial oxygen saturation of 67 per cent at rest and 48 per cent on crying. After this test the infant became deeply cyanosed and very dyspneic. At this time the liver was not enlarged, and there was no edema.

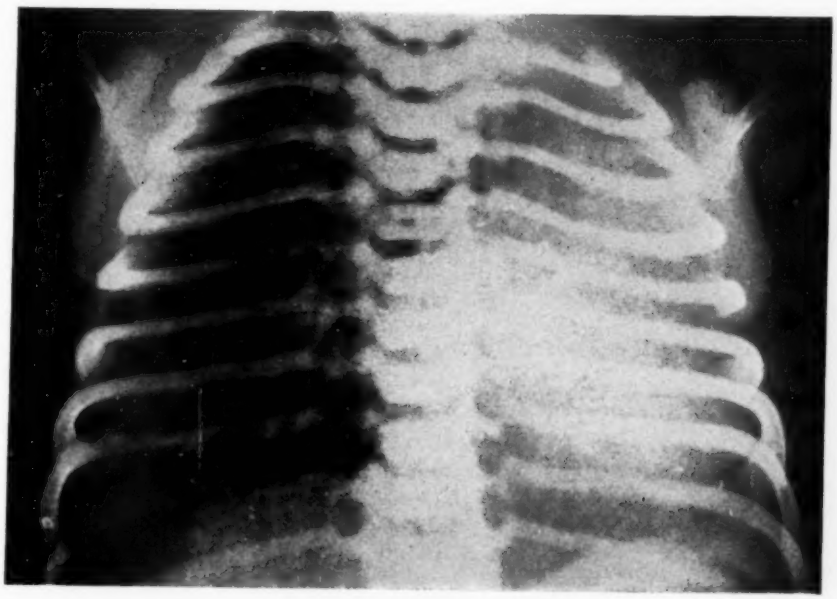

Fig. 1 (Case 1).—Anteroposterior view of chest, age 5 days.

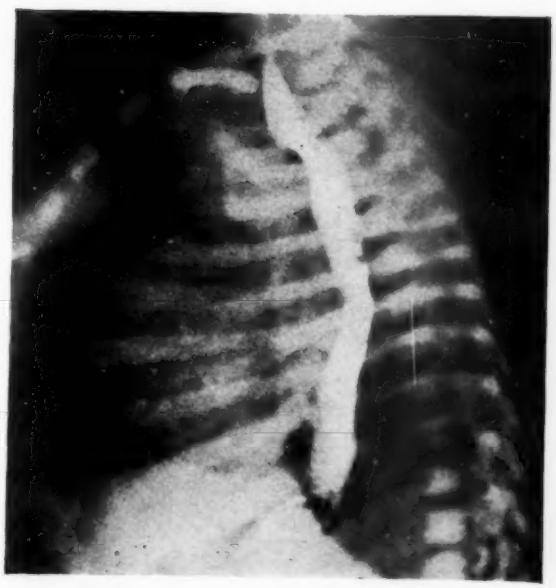

Fig. 2 (Case 1).—Left oblique view of chest with barium swallow, age 5 days.

Over the next 3 days his respirations remained gasping and cyanosis was still marked. The poor air entry and impaired percussion note over the left chest remained unchanged. Fluid intake was maintained by the interstitial route.

By the eleventh day of life a slow improvement was noted. Cyanosis was only slight while in oxygen, and the respirations were normal at rest. The systolic murmur had become louder and could not be localized to any particular intercostal space. The second sound at the base of the heart was accentuated, and the liver edge was palpable for the first time 3 cm. below the right costal margin. A second oximetric examination showed an arterial oxygen saturation of 70 per cent while in oxygen falling to 60 per cent on crying.

Oral feedings were resumed on the thirteenth day of life.

This general improvement was maintained without change in the physical signs in the chest. A bronchogram showed Lipiodol filling the bronchial tree on the right. The left main bronchus arose at a wider angle than normally, and although filling was less evident on the left, all the main branches were identified on this side (Fig. 3).

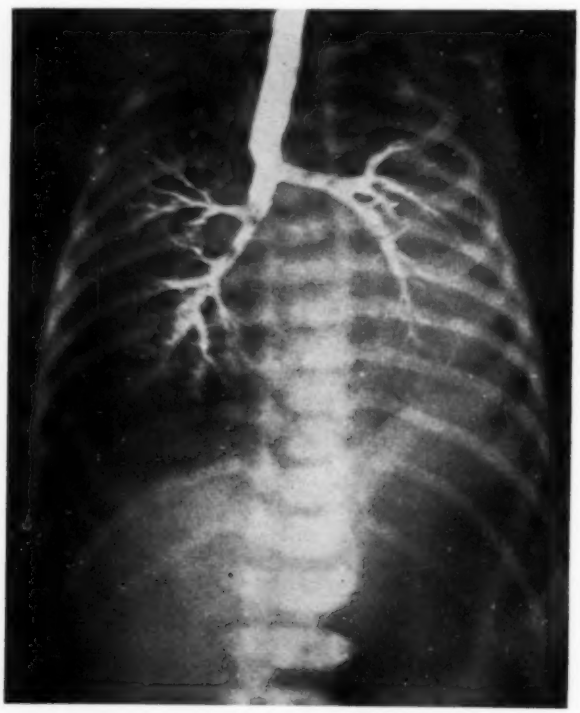

Fig. 3 (Case 1).—Bronchogram, age 14 days.

On the nineteenth day of life cyanosis and rapid shallow breathing returned. The heart rate increased and fine râles became audible at the base of the right lower lobe. The liver edge was palpable 5 cm. below the right costal margin and generalized edema appeared. At fluoroscopy the heart appeared grossly enlarged, but the left cardiac border could not be outlined. Digoxin, two intramuscular doses of $\frac{1}{8}$ mg., 8 hours apart, and Thiomerin $\frac{1}{2}$ c.c. were administered with some initial benefit to this failure. The heart rate slowed, and the edema and dyspnea were reduced.

On the twenty-first day fever and frequent loose stools appeared. By the twenty-fourth day these signs were marked and vomiting had become severe. Cyanosis returned and respirations became gasping. The apex rate was 140 per minute. There was no clinical evidence of respiratory infection. The infant died undramatically on the same day.

Serial electrocardiograms were performed during life (Fig. 4 *A* and *B*). The tracing at 5 days shows a normal sinus rhythm with a rate of 180 per minute. The P waves in Leads II and

aV_F are peaked and 2 mm. high. This latter finding is present in all recorded chest leads. The P-R interval is 0.10 second. Right axis deviation is present, the QRS axis being around +140 degrees. The duration of the QRS is 0.06 second. The right chest leads show predominant upright R waves in RV_3, V_1 and V_2, transitional complexes in V_4 and V_5 and a deep S wave in V_6. The R/S ratio in V_1 is 10/0.5(20) and in V_6 is 6.5/13.5(0.48). RV_1 plus S_{V6} totals 23.5 mm. R/Q in aV_R is 8/2.5(3.2). The T wave is low upright in Lead I and aV_L and upright in all chest leads. The Q-T_c interval is 0.380. The electrical position of the heart is horizontal. It is considered that this tracing is within normal limits for age apart from upright T waves in the right precordial leads.

At 9 days the electrocardiogram is abnormal and shows signs suggesting right ventricular hypertrophy, namely: QRS axis +180 degrees, and an R/S ratio in V_6 of 2.5/11.5(0.21). Other changes include inverted T waves in Leads II, III and aV_F. The T waves in the right precordial leads remain upright and the Q-T_c interval is 0.370.

At 13 days in addition to further progression of the right ventricular hypertrophy as evidenced by the R/S ratio in V_6 (0.07) there are changes compatible with heart failure. The T wave is inverted in Leads I, aV_L, V_5, and V_6. Notched R waves in RV_3, V_1 and V_2 may indicate right ventricular dilatation from secondary diastolic overloading. (At this time there was no clinical evidence of cardiac decompensation). The voltage is generally increased and the Q-T_c interval is lengthened to 0.490.

The last electrocardiogram on the twenty-first day, 24 hours after digitalization, shows atrioventricular dissociation with a ventricular rate of 120 per minute, and possible evidence of subendocardial ischemia. These findings suggest toxic effect from Digoxin. There is a reduction of voltage, persistence of signs of right ventricular hypertrophy, and shortening of the Q-T_c interval in addition. The notching in the R waves over the right precordium has disappeared as has the deep T-wave inversion in V_5 and V_6. These signs probably indicate benefit from Digoxin therapy. Clinically, the apex rate had slowed at this time and occasional premature beats were heard on auscultation. Digoxin was then reduced to a maintenance dosage of 1/18 mg. per day.

When the chest was opened at autopsy, the heart seemed to occupy all of the left chest but on inspection posteriorly in the upper third of the pleural cavity a small unfissured left lung was found. The right lung consisted of five portions (Fig. 5). The upper and middle lobes were normal. A deep fissure separated a superior segment from the rest of the lower lobe. An accessory lobe lay inferomedially. The right bronchial architecture was normal except for an additional branch passing to the inferomedial lobe. The left main bronchus was slightly narrowed. Thereafter, division occurred in the usual manner to the upper, middle, and lower portions of the left lung. The remaining two-thirds of the left pleural cavity were occupied by the heart.

On opening the pericardium the two major vessels appeared to arise in the normal fashion, the pulmonary artery emerging to the left anteriorly, the aorta passing to the right posteriorly. The systemic venous return was normal. From the right lung the superior pulmonary vein drained the upper two lobes and the inferior the three lower lobes. From the left lung a single pulmonary vein emerged at the hilus. These vessels emptied in normal fashion into the left auricle. The aortic arch and descending aorta lay on the right side of the spine. Of the main aortic branches the first was the common origin of the right common carotid, left common carotid, and left subclavian arteries. The second orifice was the right subclavian artery. The ductus arteriosus was absent. Both auricles seemed enlarged, the right more so than the left. There was an unsealed foramen ovale. The valve flap was fenestrated along its lower anterior and upper posterior margins. The coronary sinus was normal. The mitral and tricuspid valves were normal. Both ventricles showed marked hypertrophy, the right being thicker than the left (measurements: right ventricle 10 mm., left ventricle 8 mm.). The ventricular septum was also very thick—7 to 15 mm. A high, fairly large (9x7 mm.) defect was visible in its superior part. No membranous portion was present. The papillary muscles in the right ventricle were grossly thickened and hypertrophied. A common exit orifice guarded by 4 cusps (two right and two left) overrode the ventricular septal defect. The internal circumference of this vessel at the valvular ring measured 27 mm. A common trunk extended for 6 mm. before the main pulmonary artery emerged from the right anterior aspect (Fig. 5). The pulmonary artery was one-third the size of the systemic trunk and spiralled round the latter to a left posterior position

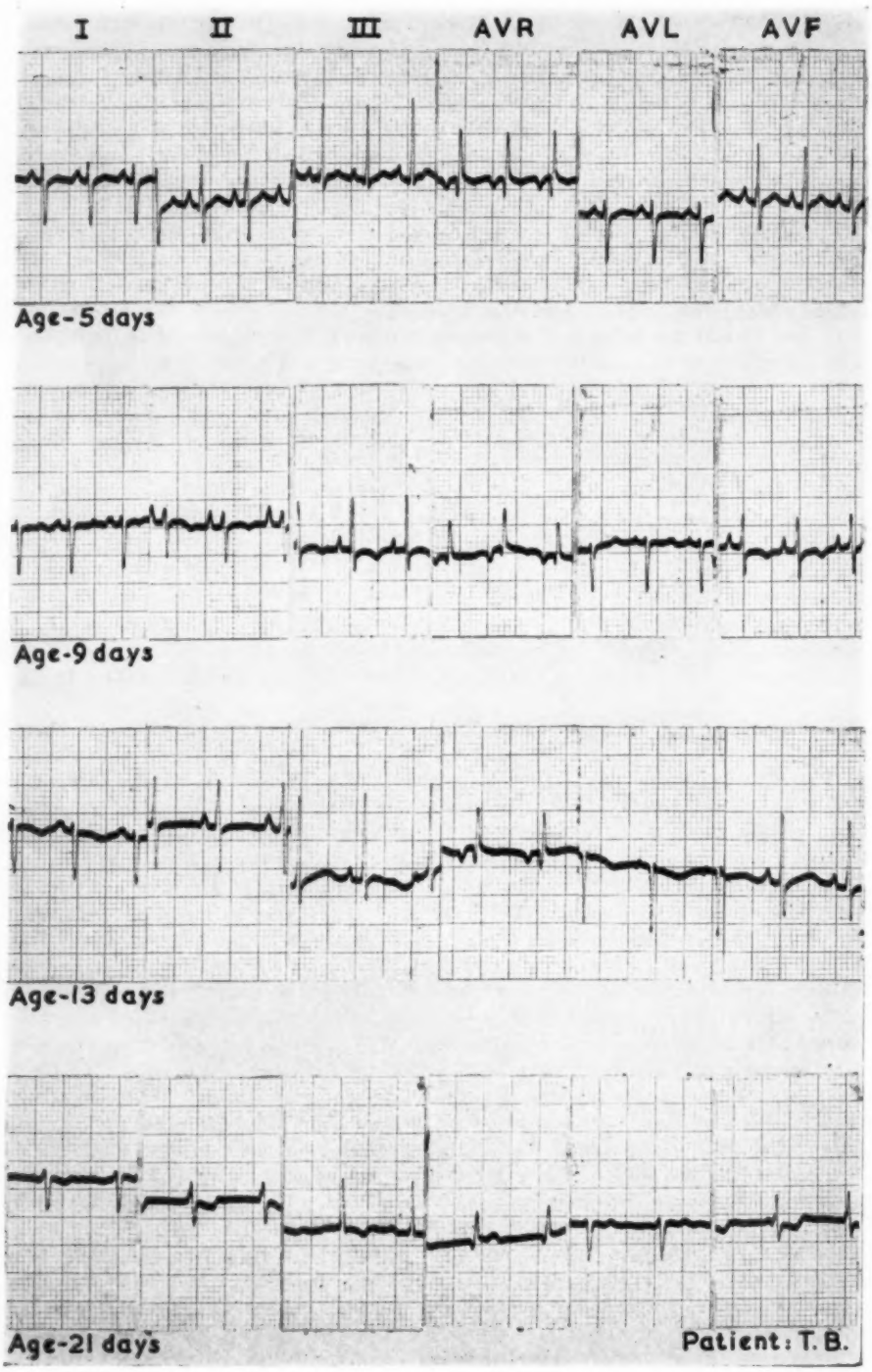

Fig. 4 (Case 1)—A.—Electrocardiogram: Limb leads at age of 5, 9, 13, and 21 days.

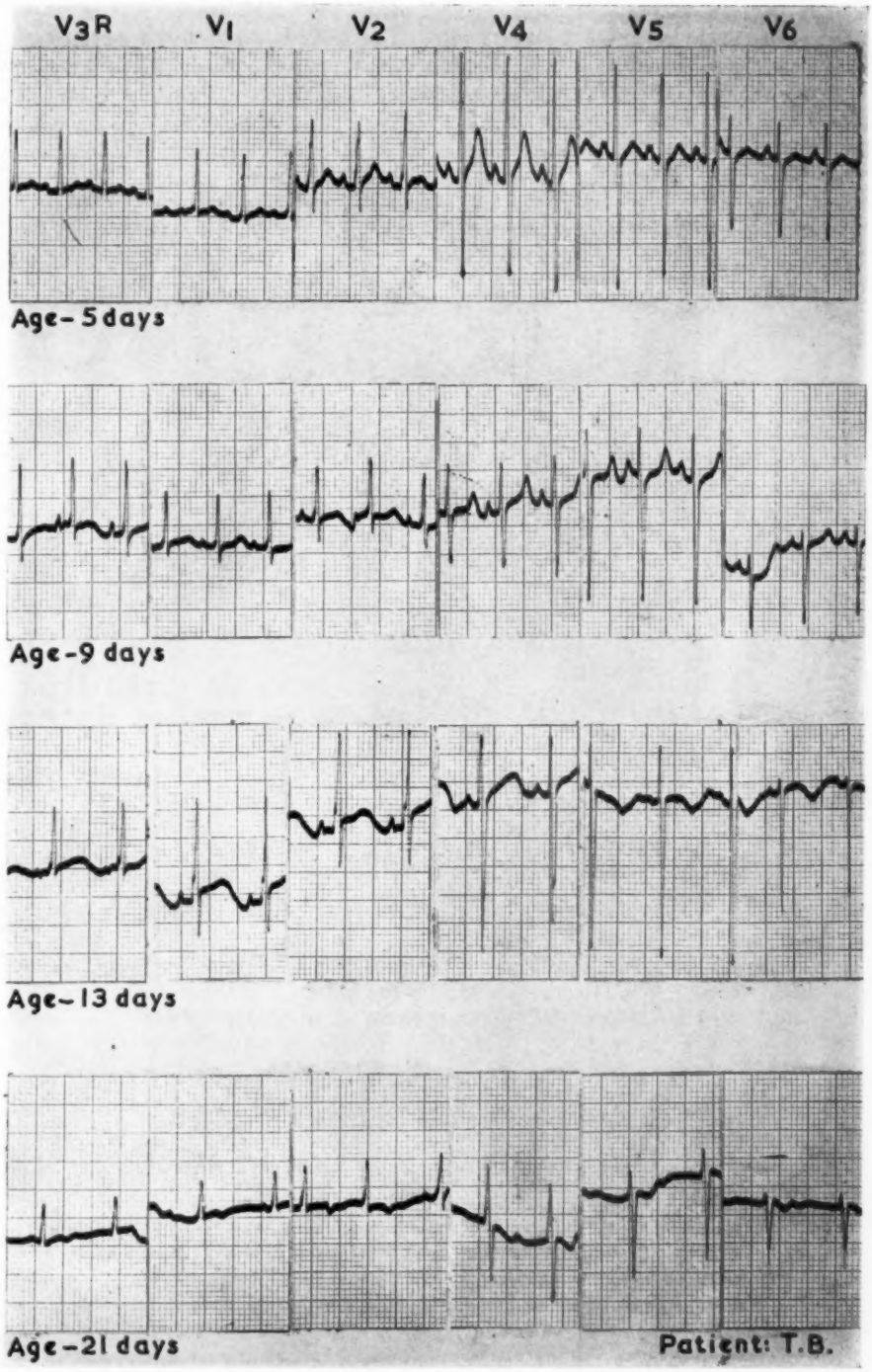

Fig. 4 B.—Electrocardiogram: Precordial leads at age of 5, 9, 12, and 21 days.

before branching. The right pulmonary artery was about four times larger than the left branch. The larger aortic portion of the truncus overrode mainly the left ventricle. The pulmonary portion overlooked the right ventricular cavity only. The right coronary artery arose above the right posterior cusp of the common orifice. The left coronary artery arose above the commissure of the left anterior cusp. No obvious branching abnormalities were noted.

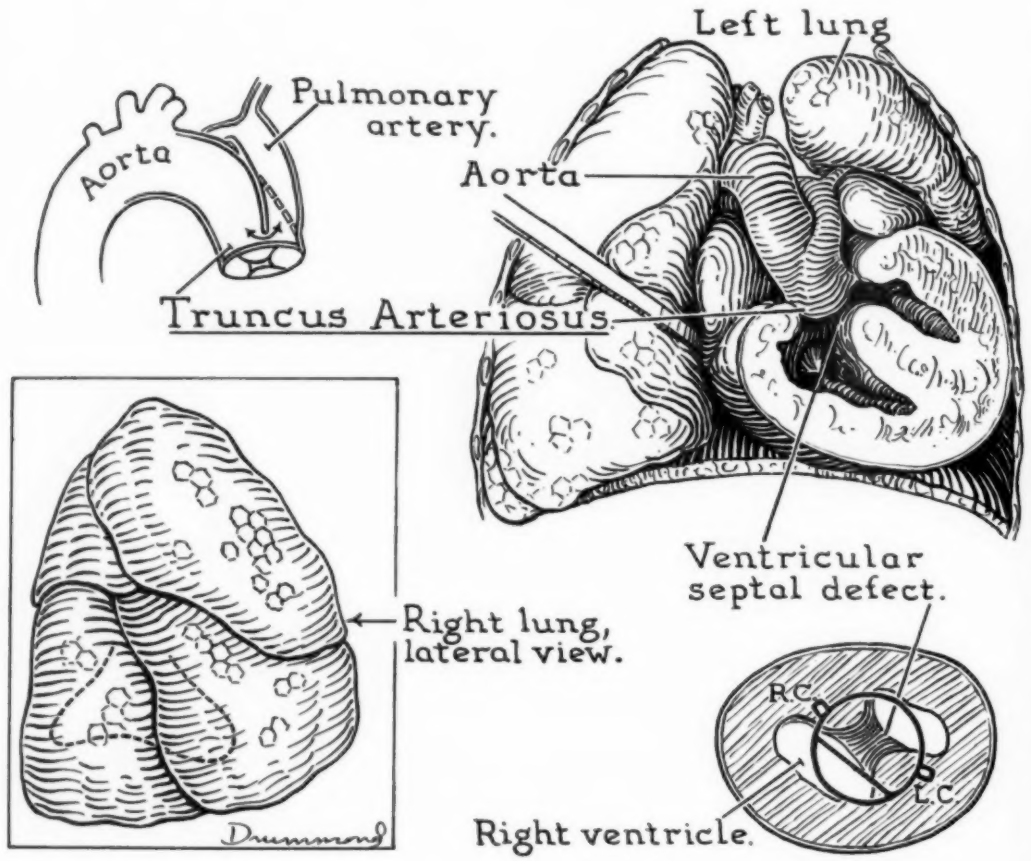

Fig. 5 (Case 1).—Drawings at autopsy. T. B. Age: 24 days.

At microscopy the left lung showed features of primary atelectasis. In addition to this lack of aeration there were amounts of granular coagulum and numbers of mononuclear cells present. The small vessels appeared normal.

Apart from a multilobed spleen and an accessory spleen no further abnormalities were encountered at necropsy.

Case 2. S. F., one of white twin girls, was born at term, Aug. 14, 1952. The birth weight was 6 pounds 11 ounces. Twin brothers had been born two and one-half years previously. Each twin was apparently normal at birth but this infant was found to have a cardiac murmur when examined at 6 days of age. She failed to gain weight normally and on the day of admission, at 4 weeks of age, she became cyanosed and dyspenic for 20 minutes.

In the Hospital for Sick Children she appeared thin, weighing 6 pounds 12 ounces and had a weak cry. There was slight generalized cyanosis with crying. The thoracic cage was normal, and the apex rate was 150 per minute. A fairly loud harsh diffuse systolic murmur was audible

over the precordium, maximal at the third to fourth left intercostal space. The second sound at the base was accentuated. Both femoral arteries were palpable. There was no clinical evidence of heart failure.

Fluoroscopy showed a moderately enlarged heart with a downward pointed apex extending almost to the chest wall. There was a slightly convex left border and a prominent vascular contour in the region of the superior vena cava. The pulmonary vascular markings were somewhat increased but no hilar pulsations could be detected. Barium swallow showed a right aortic arch.

A roentgenogram (Fig. 6) of the chest shows the transverse diameter of the heart to measure 6.9 cm. and the internal diameter of the chest 10.2 cm. The hilar shadowing appeared greater than on fluoroscopy.

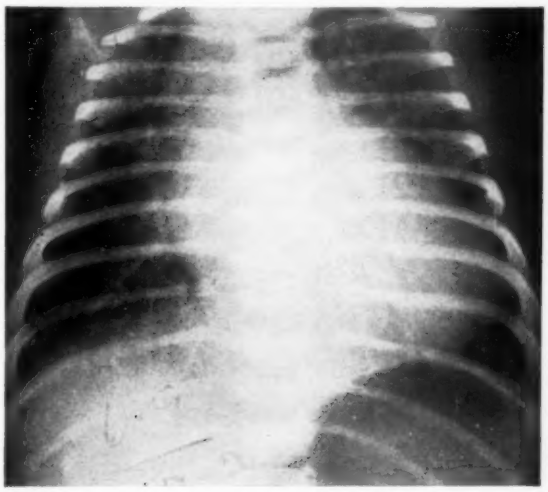

Fig. 6 (Case 2).—Anteroposterior view of chest, age 1 month.

Oximetry revealed an arterial oxygen saturation of 95 per cent at rest, falling to 87 per cent after crying.

An electrocardiogram (Fig. 7) shows regular sinus rhythm with a rate of 155 per minute. The P waves in Lead II measure 1.5 mm., are isoelectric in Leads III and aV_F, and are pointed diphasic in V_1 and V_2. The P-R interval is 0.12 second. The electrical position is vertical. The QRS wave has a duration of 0.04 second and an axis of about +90 degrees. The precordial leads show isodiphasic QRS waves in Leads RV_3 to V_5. Predominant R wave is present in V_6. The R/S ratio in V_1 is 12.5/10.5(1.19) in V_5 to 9/7.5(1.2) and in V_6 to 10/2 (5). RV_1 plus S_{V6} totals 14.5 mm. R/Q in aV_R is 2/6(0.33). There is slight depression of the S-T segment in aV_L and V_4. The T waves are inverted in Leads I, aV_L, V_4, V_5 and V_6 and low upright in aV_R. The Q-T_e interval is 0.380 second. It is considered that this tracing shows left ventricular hypertrophy in a heart of vertical position with clockwise rotation and probable right auricular hypertrophy.

A venous angiogram was performed with films taken simultaneously in anteroposterior and right lateral views at a speed of 6 per second. Dye entered the right auricle and right ventricle rapidly and at 0.8 second from the beginning of the injection the aorta and pulmonary arteries filled (Fig. 8, *a*).

The aorta passed to the right while the pulmonary artery seemed small. After 0.85 second (Fig. 8, *b*) better filling is observed. The descending aorta is visible on the right, and the dye leaves the right ventricle in a large vertical column. Both the aorta and the pulmonary artery seem to continue from this trunk. A very constant finding in both anteroposterior and lateral films up to 2 seconds was an irregular horizontal contour about 1 cm. from the superior angle of the tricuspid ring. The clear V shaped angle, in the anteroposterior view marking the deviation of aorta and pulmonary artery at a level of 1 cm. above the aforementioned horizontal line, is also visible in lateral films. Small vessel filling within the lungs is scanty.

The child was discharged from the hospital, and the status remained unaltered for the next 3 months. After a brief episode described as pneumonia she died in another hospital on Dec. 1, 1952. The preserved specimen with the great vessels limited to 3 cm. from the base of the heart is available (Fig. 9).

The heart is markedly enlarged and egg-shaped. Its long diameter measures 6.5 cm. Lying at the extreme right is a large right auricle. The anterior aspect of the ventricular mass is divided by the interventricular sulcus into two unequal portions—a large right area corresponding to the right ventricle and a smaller left (about one-third the size of the former) belonging to the left ventricle. The apex and the left border of the heart are entirely formed by the systemic ventricle and its upper aspect presents a fairly marked convex shoulder. At the base lying between the left ventricular shoulder and the great vessels is the left atrial appendage. Two great vessels appear to arise at the base of the heart, a relatively large right-posterior aorta and a relatively small pulmonary artery situated left anteriorly. Upon opening the heart the right atrium is found to be enlarged and hypertrophied. The inferior and superior vena cava enter it normally. The foramen ovale is completely sealed. The ostium of the coronary sinus lies medially from the orifice of the inferior vena cava and is guarded by a 6 mm. long membranous valve. The left atrium is somewhat smaller than the right. Four pulmonary veins drain into it. The tricuspid and the mitral valves are normally formed. Numerous nodular thickenings occupy the margin of closure of their cusps. The right ventricle is markedly enlarged. Its walls measure only about 5 mm. in thickness but very prominent papillary muscles and trabeculae carneae are present.

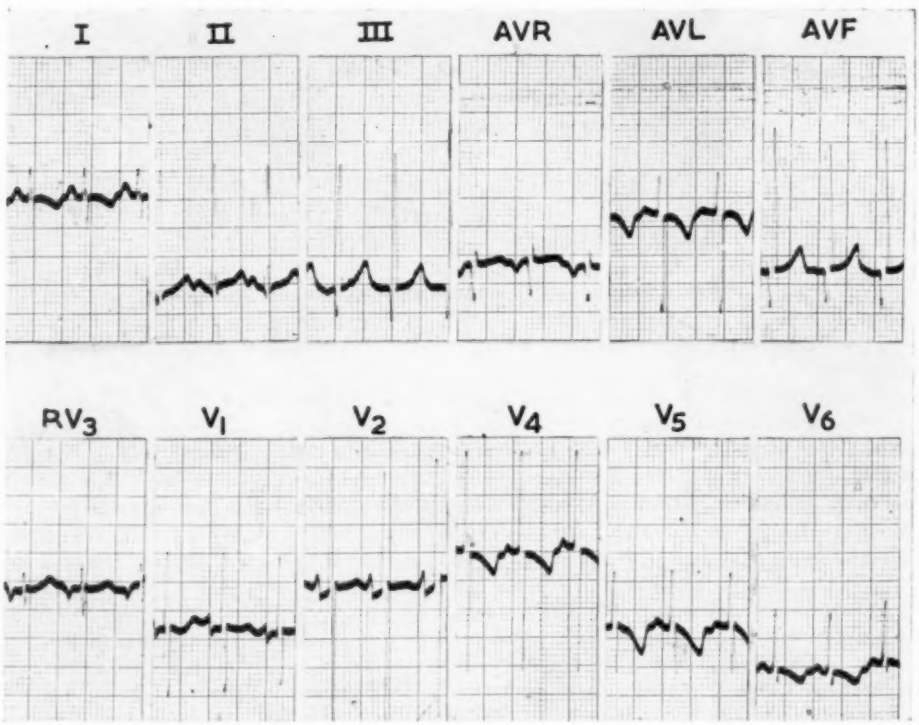

Fig. 7 (Case 2).—Electrocardiogram at age of 1 month.

The left ventricular cavity is smaller than the right, but its walls are thicker, measuring 7 to 8 mm. The ventricular septum is extremely thick, and an oval defect of about 11 by 6 mm. lies at its superior aspect. No membranous portion is present. A single exit valve common to both ventricles lies astride the interventricular septum. Its internal circumference measures 38 mm. Three, one anterior and two posterior, large, thick competent cusps guard this orifice. The coronary ostia are situated behind the posterior cusps, the right coronary artery arising from behind the right cusp and the left from behind the left. A large common arterial trunk supplying

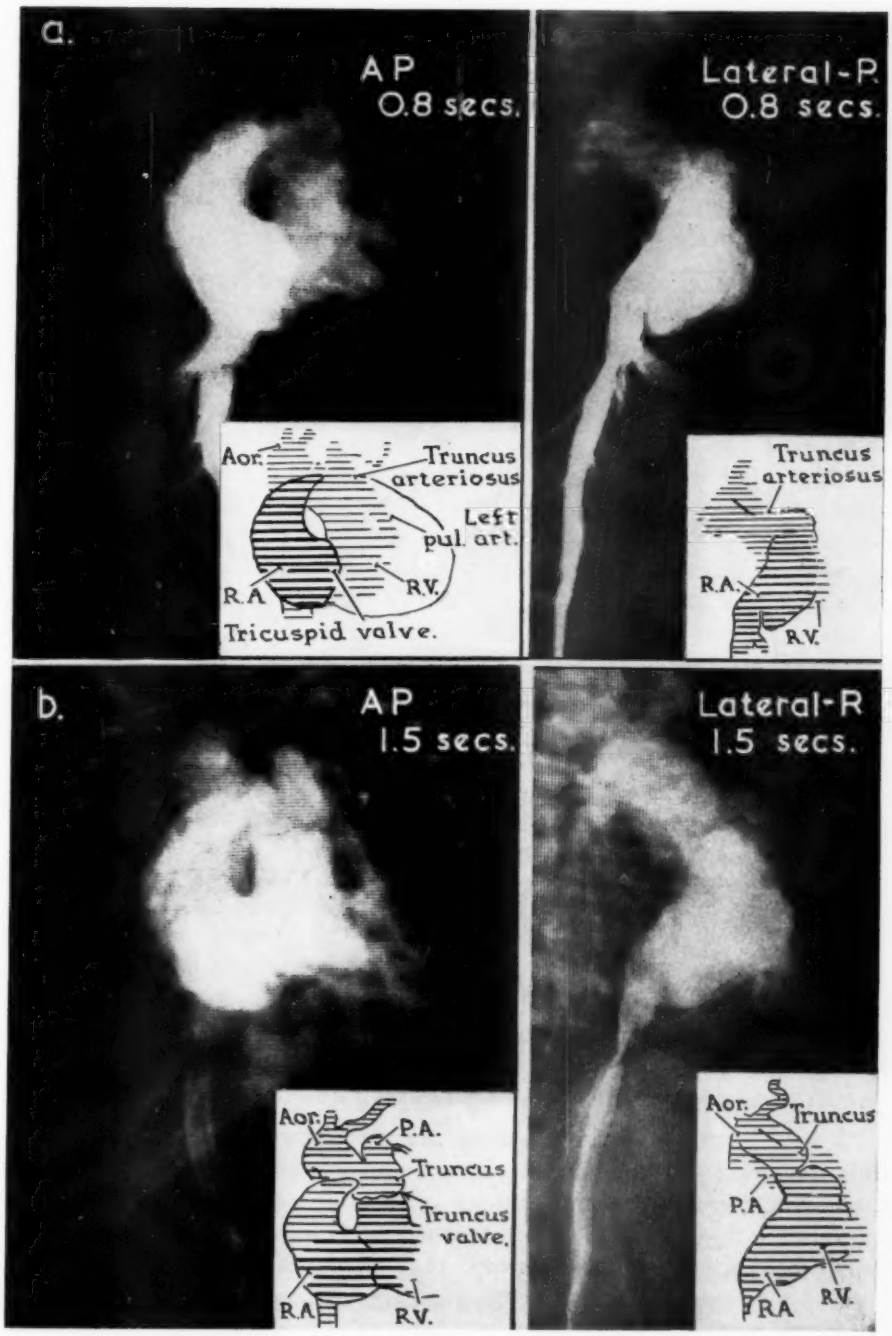

Fig. 8 (Case 2).—Venous angiogram.

both the systemic and the pulmonary circulation arises at this level. After a distance of 11 mm. it is divided by an oblique, crescentic ridge into two portions. The large posterior portion forms the ascending aorta and, 24 mm. from the truncus valve, gives off a major aortic branch anteriorly. The anterior portion is formed by what appears externally to be the pulmonary artery trunk. The internal architecture, however, shows that the two pulmonary artery branches arise separately, side by side, and then spiral in a clockwise direction. In this manner the channel which at its origin is situated on the right forms the left pulmonary artery and vice versa (Fig. 9). The right pulmonary artery branches again, well before passing beneath the aortic arch. From the anterior aspect of the right pulmonary artery 1 cm. above its origin a small, patent, thin-walled vessel arises. The future path of this vessel cannot be traced on the isolated specimen and is not included in Fig. 9.

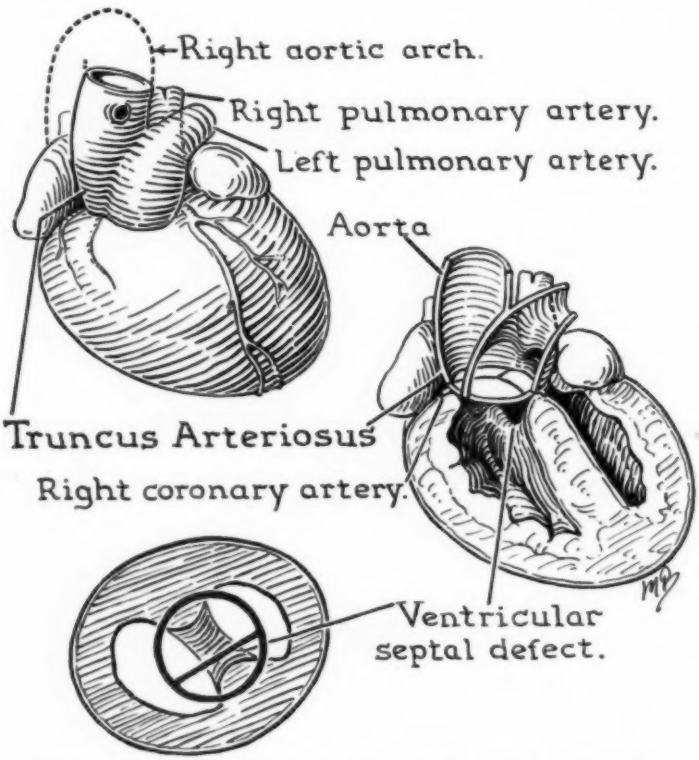

Fig. 9 (Case 2).—Drawings at autopsy. S. F. Age: 3½ months.

DISCUSSION

Physical examination in persistent truncus arteriosus in infancy classically reveals moderate or severe cyanosis, a harsh systolic, or rarely a continuous murmur over the precordium, absence of normal splitting of the second basal heart sound and marked cardiac enlargement. Fluoroscopy has revealed a characteristic cardiac outline aptly termed the "sitting-duck" contour.[4] The aortic knob is always prominent, and while the degree of lung vascularity varies, it is usually diminished. These signs could be produced by extreme tetralogy of Fallot or pulmonary atresia as well as truncus arteriosus. It is almost impossible to make the diagnosis clinically in the absence of the typical roentgenographic contour. That the latter is not invariably present is evidenced by both our

cases. In neither was the cardiac outline alone of great help, although it was suggestive in Case 1. In this patient fluoroscopy was of less help than usual because of the associated lung anomaly. In the second case the cardiac outline in its left middle arch showed a prominent convex shoulder. A similar appearance is a common finding in complete uncomplicated transposition of the great vessels[5] and has been seen in a case of endocardial fibroelastosis. In all three conditions this localized bulge was formed by the lateral wall of the hypertrophied left ventricular inflow chamber in the presence of a large and/or hypertrophied right ventricle.

Standard lead electrocardiograms have shown right-axis deviation in several reported patients and left-axis deviation in at least two instances. Our younger infant developed an increasing degree of right ventricular hypertrophy, while the older baby with an identical malformation showed left ventricular hypertrophy. It is interesting that at autopsy in each patient both ventricles were extremely hypertrophied. It will be seen in the electrocardiogram of Case 1 at 13 days that the T wave is inverted in Leads I, aV_L, V_5 and V_6 suggesting that in addition to the predominant right ventricular hypertrophy some degree of left chamber hypertrophy is present. Conversely in the electrocardiogram of Case 2 the association of left ventricular hypertrophy with a vertical electrical position, clockwise rotation and an R/S ratio in V_1 of over unity might be taken as evidence for hypertrophy of the other ventricle. It may be possible to recognize biventricular hypertrophy electrocardiographically with greater ease when more distinct criteria have been formulated for this age group. The presence of right ventricular hypertrophy in the electrocardiogram is of no real help in the diagnosis of truncus arteriosus. On the other hand, when left ventricular hypertrophy is found in conjunction with the previously mentioned physical and radiologic signs the diagnosis of truncus arteriosus can be made more confidently because of the virtually certain exclusion of pulmonary atresia or extreme tetralogy of Fallot.

The venous angiogram in our second patient reveals several interesting features, some of which will be peculiar to this particular type of the malformation and others common to all types. The common trunk is easily visualized and the pulmonary arteries are seen arising from it clearly some distance above the exit valve. It is difficult to see how angiocardiography could differentiate pulmonary atresia from truncus arteriosus where bronchial vessels form the sole pulmonary blood supply.

Our two hearts had remarkably similar anatomic features, namely, right aortic arch, equal degree of overriding of the ventricular septal defect by the common trunk, hypertrophy of both ventricles and the low origin and reduced size of the pulmonary arteries. In both, the latter vessels arose right anteriorly and passed in a spiral manner upwards and to the left. Unusual findings were the associated hypoplasia of the left lung in Case 1 and the peculiar geminate origin and course of two independent pulmonary arteries in Case 2. It would appear that neither of these latter details have been encountered previously.

SUMMARY

Two infants with persistent truncus arteriosus and right aortic arch proved by autopsy are described from their clinical and pathological aspects.

The electrocardiogram shows in one case predominant right ventricular hypertrophy and in the other case predominant left ventricular hypertrophy, but both have features suggesting biventricular hypertrophy.

A venous angiogram in one case reveals clear evidence of the malformation.

Dr. Wilford Waite of Brantford, Ont., kindly sent us the specimen in Case 2. We are indebted to Dr. J. D. Keith, Chief of the Cardiac Service, for helpful criticism, and to Miss M. Drummond and Mrs. G. Clawson of the Department of Visual Education, Hospital for Sick Children, for their valuable assistance.

REFERENCES

1. Collett, R. W., and Edwards, J. E.: Persistent Truncus Arteriosus: A Classification According to Anatomical Types, S. Clin. North America **29**:1245, 1949.
2. Taussig, H. B.: Clinical and Pathological Findings in Cases of Truncus Arteriosus in Infancy, Am. J. Med. **1**:26, 1947.
3. Dotter, C. T., and Steinberg, I.: Angiocardiography, Annals of Roentgenology, **20**:229, 1951.
4. Brown, J. W.: Congenital Heart Disease, London, 1950, Staples Press, Ltd., p. 244.
5. Keith, J. D., Neill, C. A., Rowe, R. D., Vlad, P., and Chute, A. L.: Transposition of Great Vessels, Circulation: (in press), 1953.

Clinical Reports

VENTRICULAR FIBRILLATION FOLLOWING THE ADMINISTRATION OF ACETYL STROPHANTHIDIN

ZEB L. BURRELL, JR., M.D. AND ROBERT P. COGGINS, M.D.

AUGUSTA, GA.

ALTHOUGH ventricular fibrillation is usually mentioned as being the most important single cause of death in any discussion of digitalis intoxication there are few recorded cases with electrocardiographic substantiation. We were able to find seven cases from the literature with graphic illustration of ventricular fibrillation apparently caused by digitalis intoxication.

Reid[1] in 1924 described a case of ventricular fibrillation occurring in a patient with auricular fibrillation who was given excessive amounts of tincture of digitalis. In this case the change was from auricular fibrillation to electrical bigeminy (bidirectional ventricular tachycardia) with abrupt change to ventricular fibrillation. A case of ventricular fibrillation occurring in a patient approximately one minute after the injection of an unstated amount of ouabain was reported by Tandowsky and associates.[2] Beck and associates[3] reported a case of successful defibrillation by electric shock, the fibrillation following the administration of 1.6 mg. lanatoside C to a patient for tachycardia developing during anesthesia. Two cases were reported in European journals in 1933 and 1935.[4,5] Both of these cases followed the administration of strophanthidin. The first of these followed some hours after the administration of 0.125 mg. strophanthidin to a patient who had shown digitalis bigeminy some six days earlier. In this case the electrocardiogram just prior to death showed ventricular tachycardia terminating in fibrillation. The second of these cases showed a merging of ventricular tachycardia and fibrillation in several places throughout the record, and although the fibrillation was controlled by the intracardiac injection of magnesium sulfate the patient died within a few hours. Enselbergh and associates[6] reported two cases of fibrillation following the administration of acetyl strophanthidin. The first of their cases was fatal, the ventricular fibrillation beginning some six minutes after the injection of 1.2 mg. of acetyl strophanthidin intravenously in a patient who was in failure with a myocardial infarction of some five days duration. All

From the Department of Internal Medicine and the Cardiac Clinic of the University Hospital and Medical College of Georgia.

Received for publication Feb. 6, 1953.

electrical activity ceased some twenty-three minutes after the injection. The second case followed the administration of 1.2 mg. of the drug to a patient with intractable heart failure, first occurring some ten minutes after injection and lasting for approximately ten seconds with a second episode of approximately thirty seconds duration some fifteen minutes after injection. There was return to the preinjection state within forty-five minutes after the administration.

CASE REPORT

A 72-year-old Negro woman was admitted to the University Hospital from the emergency room at 6:30 P.M., September 20, 1952 in a semistuporous state. She had been followed in the outpatient department for a number of years, and according to the outpatient records she had been maintained on 100 mg. digitalis leaf daily for some years.

During the week prior to admission she had had increasing shortness of breath and pain in the epigastric region. She had been seen in the emergency room two nights prior to admission. At that time she complained of shortness of breath and nausea. She was given aminophyllin, aluminum hydroxide gel, and belladonna at that time and advised to attend the outpatient department on the following day. She did not keep the appointment. On the evening of admission she was found in a semistuporous condition by a neighbor and was brought to the emergency room.

Examination at the time of admission revealed temperature 98.8° F., pulse 148 beats per minute, respiration 28 per minute, and blood pressure 190/120 mm. Hg.

She was well developed, fairly well nourished, and appeared approximately the recorded age. She was sitting in a semiupright position; her sensorium was cloudy, and she responded very poorly to stimuli. The skin was dry and loose. The nail beds and mucous membranes were moderately cyanotic. The fundi showed arteriovenous nicking and tortuosity of vessels. The neck veins were markedly distended. No tracheal tug was present. Respiration was labored. The lungs were clear to palpation and percussion. There were medium moist râles over both bases, more pronounced posteriorly. The heart was enlarged to the anterior axillary line on the left. The apex impulse in the seventh intercostal space at the anterior axillary line was rapid and forceful. No thrills were felt. There was a soft, blowing systolic murmur at the apex. The abdomen was flat. No tenderness, rigidity, masses, or fluid were present. No organs were palpable. There was no sacral or pedal edema. The peripheral pulse was regular, rapid, and forceful. Reflexes were physiological, and no pathological reflexes were present. Clinical impressions were: (1) hypertensive cardiovascular disease, (2) congestive heart failure, moderate, and (3) aneurysm of the aorta to be ruled out.

Electrocardiogram at this time (Fig. 1) was interpreted as an abnormal record showing: (1) sinus tachycardia with a rate of 148 per minute, (2) left ventricular hypertrophy and/or strain, (3) horizontal position, and (4) questionable digitalis effect.

Following admission at 6:30 P.M. the patient was given 0.4 mg. lanatoside C intravenously, oxygen by nasal catheter bubbled constantly, through alcohol,[7] and 120 mg. sodium phenobarbitol intramuscularly. Approximately one hour later she was given 0.5 Gm. aminophylline intravenously. In spite of this treatment her condition had changed little after four and one-half hours and it was thought necessary to give additional digitalis. Because of its reported margin of safety and rapidity of excretion it was felt that acetyl strophanthidin would be the ideal drug in view of the unknown extent of digitalization. Six hours after admission a direct writing electrocardiogram still showed no digitalis effect (Fig. 2, 1), and 0.5 mg. of acetyl strophanthidin was given intravenously over a period of approximately five minutes. At the completion of injection an electrocardiogram (Fig. 2, *2*) showed no change. A tracing made one minute following completion of injection (Fig. 2,*3*) showed no change. Between one and two minutes following completion of injection the patient suddenly gasped, and the hitherto prominent carotid artery pulsations were observed to be no longer present. The electrocardiograph was immediately turned on and confirmed the presence of ventricular fibrillation. The patient made only two or three gasping respiratory efforts and all electrical activity had ceased some six minutes after the completion of injection, there being no further complexes other than those of fibrillation (Fig. 2, *4* to *9*). Permission for autopsy was not obtained.

COMMENT

In discussing their two cases and analyzing the other cases appearing in the literature, Enselberg and associates[6] describe what is called a prefibrillatory state which occurs in the majority of these patients. This state consists of ventricular premature beats, coupling, polymorphism, runs of ventricular extrasystoles, and paroxsyms of ventricular tachycardia. By watching for these signs of ventricular hyperirritability it should be possible to prevent the catastrophe of ventricular fibrillation.

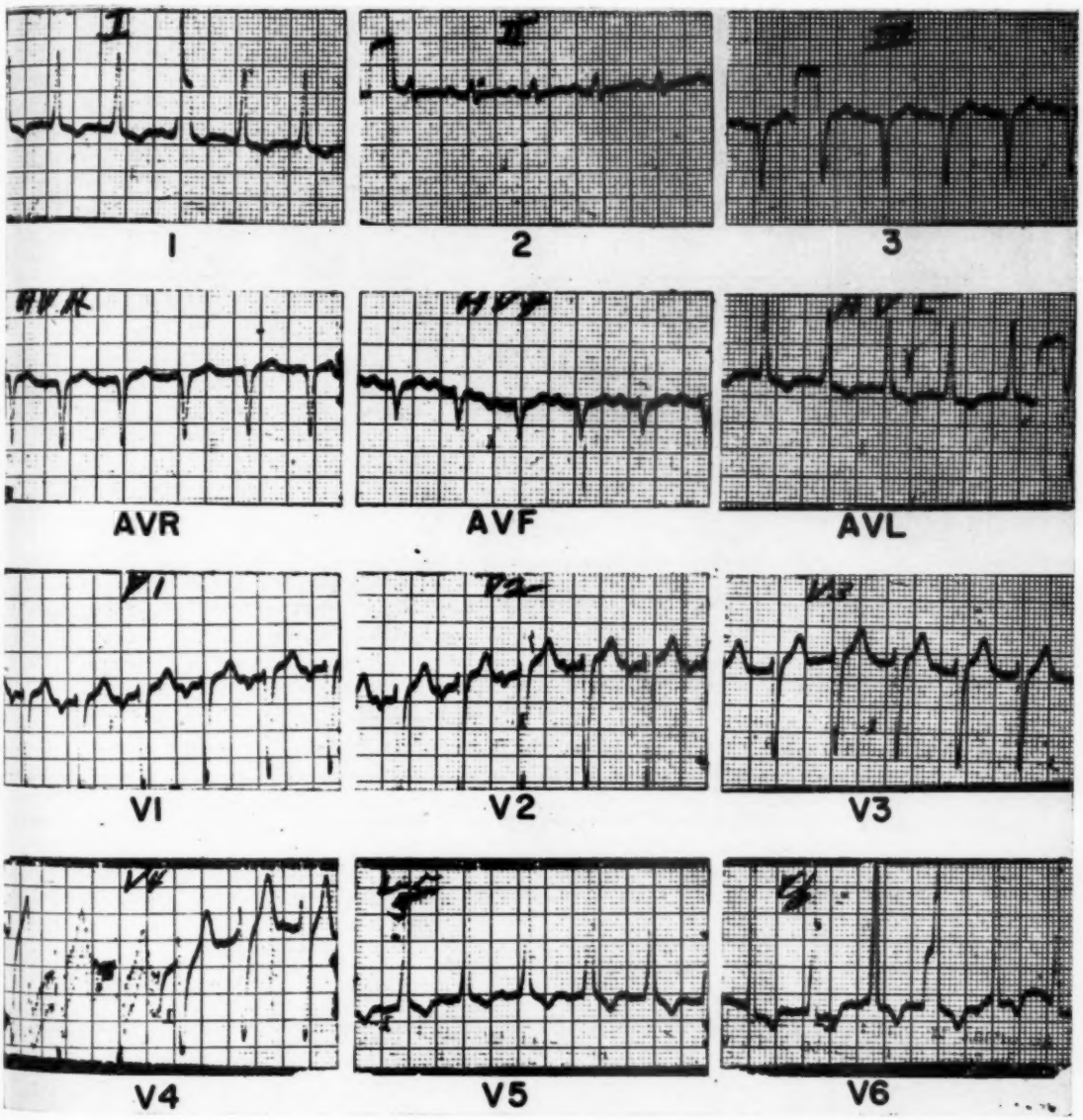

Fig. 1.—Electrocardiogram at time of admission.

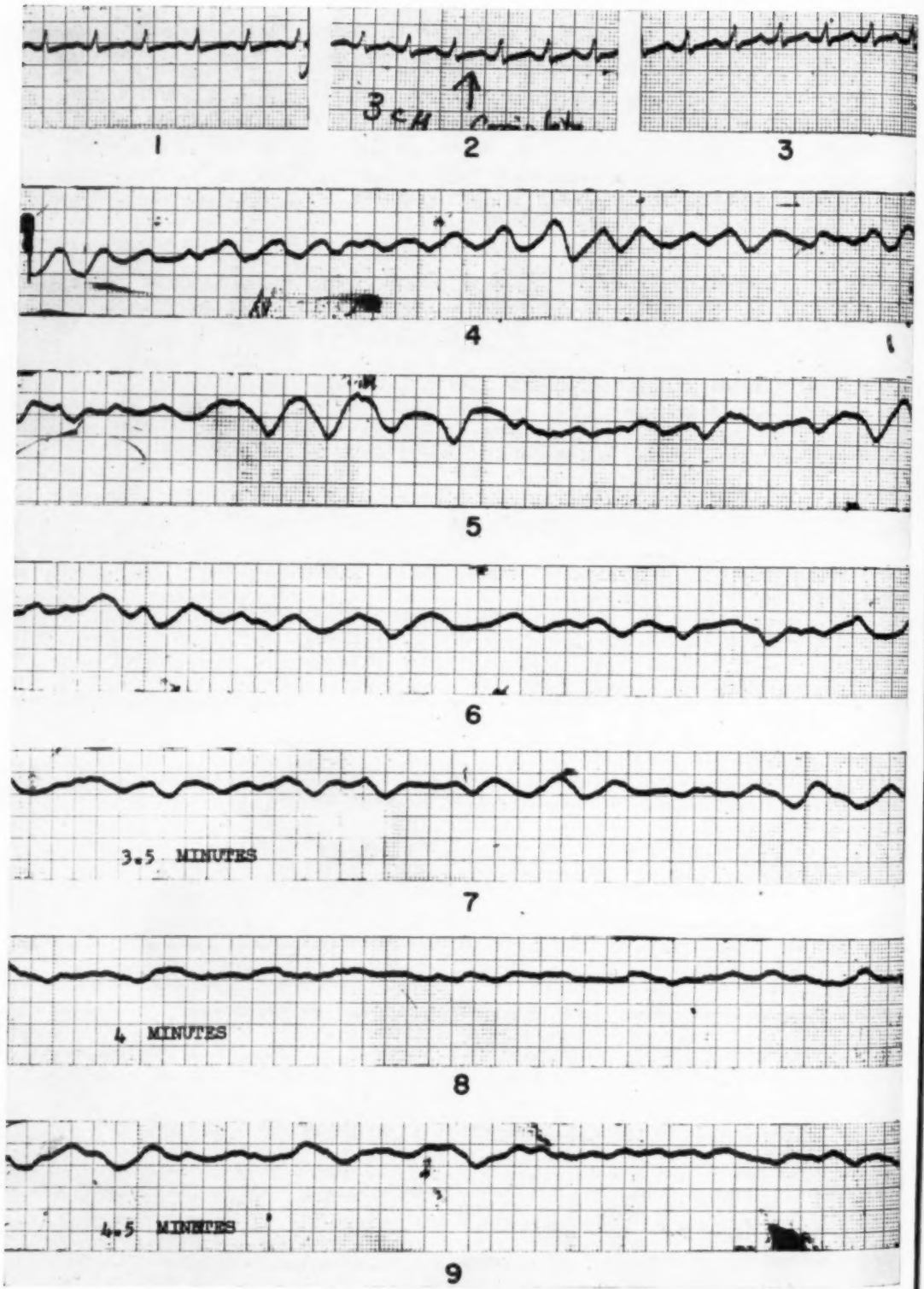

Fig. 2.—*1.* Prior to injection of 0.6 mg. acetyl strophanthidin. *2.* At completion of injection. *3.* One minute following completion. *4.* Approximately two minutes following completion of injection. *5-9.* Thirty second intervals following 4.

It is of note that these signs were not observed in our case. There were none of these warnings present prior to injection, at the completion of injection, and one minute following completion of injection. Shortly after the electrocardiograph was turned off following the one-minute tracing the patient gasped with the clinical onset of fibrillation. The machine was turned on immediately and the tracing showed ventricular fibrillation. If a prefibrillatory state existed in this case it was certainly of short duration—probably less than thirty to forty-five seconds.

The various ventricular arrhythmias are known to predispose to ventricular fibrillation and therefore offer a contraindication to the use of the rapid acting digitalis preparations, but the occurrence of such accidents even in the absence of contraindications makes it obvious that such can be prevented only by refusal to use the rapid acting intravenous preparations when any of the more conservative preparations will suffice.

SUMMARY AND CONCLUSIONS

1. Seven cases from the literature of ventricular fibrillation with electrocardiographic substantiation, apparently from digitalis intoxication, are briefly presented.

2. An additional case of ventricular fibrillation from acetyl strophanthidin with no apparent prefibrillatory state is reported.

3. It is concluded that such accidents can be avoided only by the refusal to use rapid acting digitalis preparations when a slower preparation will suffice and that the previously stated contraindications and warning signs are not always reliable.

REFERENCES

1. Reid, W. D.: Ventricular Fibrillation Following Ectopic Ventricular Tachycardia, Boston M. & S. J. **190**:686, 1924.
2. Tandowsky, R. M., Anderson, N., and Vandeventer, J. K.: An Electrocardiographic and Clinical Study of Various So-called Cardiac Drugs, Am. Heart J. **28**:298, 1944.
3. Beck, C. S., Pritchard, W. H., and Feil, H. S.: Ventricular Fibrillation of Long Duration Abolished by Electric Shock, J. A. M. A. **135**:985, 1947.
4. Penati, F.: Electrokardiographicher Befund von Herzflimmern bei plotzlichem, Herztod. Klin. Wchnschr. **12**:1249, 1933.
5. Zwillinger, L.: Ueber die Magnesiumwirkung auf das, Herz. Klin. Wchnschr. **14**:1429, 1935.
6. Enselberg, C. D., Croce, J. P., and Lown, B.: Ventricular Fibrillation Due to Digitalis Preparations, Circulation **3**:647, 1951.
7. Luisada, Aldo A., Goldmann, M. A., and Weyl, Ruth: Alcohol Vapor by Inhalation in the Treatment of Acute Pulmonary Edema, Circulation **3**:363, 1951.
8. Schwartz, S. P., and Jezer, A.: The Effects of the Intravenous Administration of Digitalis Bodies on Patients With Transient Ventricular Fibrillation, Am. Heart J. **16**:462, 1938.

COMBINED MITRAL AND PULMONARY ATRESIA

CONRAD R. LAM, M.D., E. M. KNIGHTS, M.D., AND R. F. ZIEGLER, M.D.

DETROIT, MICH.

CONGENITAL mitral atresia is itself a rare anomaly and its combination with pulmonary atresia has not been reported previously. The possibility of an infant surviving the neonatal period with no clear-cut way of blood reaching the lungs or leaving them would have seemed extremely remote. Nevertheless, this child was able to exist for three months, at which time operative intervention to relieve the cyanosis was attempted.

In Abbott's atlas[1] which presents an analysis of 1,000 cases are listed five cases of mitral atresia. Concomitant defects were patent ductus arteriosus (2 cases) and atrial septal defects (4 cases). There was no instance of associated atresia or stenosis of the pulmonary artery; in fact, in three cases the pulmonary artery was said to be dilated.

Taussig's book[2] was consulted and only two cases of mitral atresia were noted. Associated defects in an infant dying at 5 days were widely patent foramen ovale and aortic atresia; the pulmonary artery was normal. The second infant died at the age of 10 weeks and examination of the heart showed mitral atresia, a single ventricle with transposition of the aorta and pulmonary artery, and a small opening in the auricular septum.

CASE REPORT

K. B., a white baby girl, was first seen at the age of 7 weeks for the evaluation of cyanotic congenital heart disease. The family history was negative with respect to the health of two siblings, any familial history of congenital defects or maternal illness during pregnancy. The patient was born by breech delivery at full term and had had constant cyanosis since birth. In addition, there was persistent hyperpnea with periodic episodes of increased dyspnea and cyanosis but no limpness or loss of consciousness. Growth and development were fairly normal, her birth weight being 5 pounds 7 ounces with an increase to 7 pounds 7 ounces at 7 weeks. The initial examination revealed, in addition to the cyanosis, a moderately loud systolic murmur heard best at the base of the heart. No diastolic murmur could be heard, the femoral artery pulsations were palpable and there was no evidence of congestive heart failure. Fluoroscopic examination showed no over-all increase in the heart size and the cardiac configuration was compatible with that usually seen in tetralogy of Fallot. (Fig. 1) The lung fields were remarkably clear. The electrocardiogram displayed evidence of right ventricular hypertrophy but with a pattern which was distinctly unusual for an uncomplicated tetralogy. (Fig. 2) On the basis of this information it seemed certain that there was diminished pulmonary blood flow and an intracardiac venous-arterial shunt, so other diagnostic procedures such as cardiac catheterization and angiocardiography were thought unnecessary.

From the Departments of Surgery, Laboratories, and Pediatric Cardiology of the Henry Ford Hospital, Detroit, Michigan.

Received for publication March 12, 1953.

During the ensuing month and a half, growth rate was diminished and the baby had increasing disability with the occurrence of severe anoxic attacks with loss of consciousness. It was felt at this time that a shunting type of operation should be done in order to increase the volume of pulmonary blood flow. Accordingly, under endotracheal cyclopropane anesthesia and with cooling by means of ice bags, the usual posterolateral thoracotomy for the Pott's procedure was carried out. It was possible to create a small side-to-side anastomosis between the aorta and a markedly hypoplastic left pulmonary artery. Just as the posterior part of the suture line was completed, the heart dilated and stopped. The balance of the suturing of the anastomosis was completed as rapidly as possible and the constricting ligatures and Pott's clamp were removed. Cardiac massage was begun about five minutes after the standstill. After about 10 minutes, the heart began to beat slowly and regularly and the exposed tissues appeared less cyanotic than before the operation. No thrill could be palpated in the small pulmonary artery, but it was assumed that the anastomosis was functioning. The chest was closed and the infant returned to an oxygen incubator, with very definite improvement in color.

Immediately after the operation, a rather distant continuous murmur could be heard over the left upper chest anteriorly. The color remained improved, but the patient did not regain consciousness, a fact which was attributed to the period of asystole. Decerebrate rigidity, however, was not present. Within two hours, the continuous murmur gradually disappeared and the cyanosis returned. The left chest showed impairment to percussion and decrease in breath sounds. Thoracentesis for the relief of possible hemothorax was productive of only 7 c.c. of blood. The child expired 4 hours after the operation.

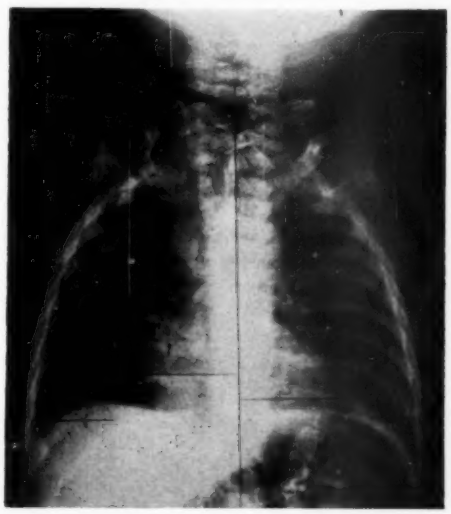

Fig. 1.—Posteroanterior roentgenogram of chest.

Necropsy.—The positive findings were confined to the thoracic cavity. The left pleural space contained about 10 c.c. of serosanguinous fluid. A slightly greater quantity of thinner fluid was present on the right. The two lungs were strikingly dissimilar in appearance. The left was dark reddish blue in color, moist and somewhat larger than the right, which was paler in color. (Fig. 3) The heart and lungs were removed in a block for more accurate dissection and evaluation. When viewed anteriorly, the right atrium and ventricle were seen to be extremely large. The left atrium and ventricle were correspondingly much smaller. Following were the findings in the dissected heart:

1. Right ventricular hypertrophy. The right ventricle was approximately six times as large as the left. The wall measured 0.6 cm. in thickness after fixation.

2. Pulmonic valve atresia. The pulmonary artery arose blindly in the anterior superior wall of the left ventricle. No valve was present. The vessel measured 0.4 cm. in diameter and was

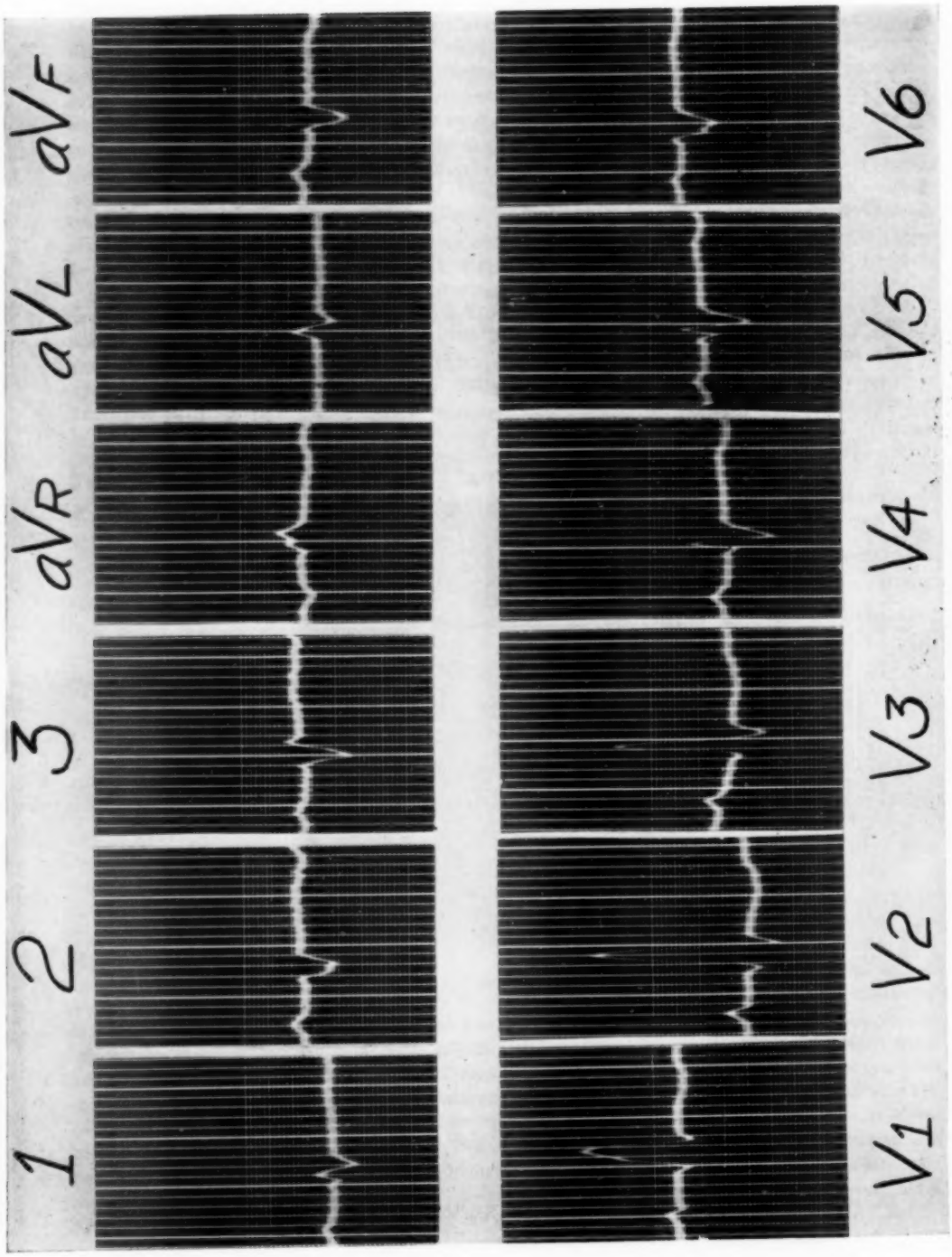

FIG. 2.—Electrocardiographic tracings. There is evidence of right ventricular hypertrophy in the unipolar precordial leads. The appearance of the Q waves in the leads from the right side of the precordium is unusual in the tetralogy of Fallot.

connected to the aorta by a ductus arteriosus of slightly smaller diameter. The end of the ductus opening into the pulmonary artery was small and barely admitted a fine probe.

3. Patent interventricular septum. There was an oval opening in the posterior superior portion of the interventricular septum measuring 0.6 cm. in greatest diameter.

4. Extreme dextroposition of the aorta. The aorta overrode the patent interventricular septum, arising more from the right than from the left ventricle and posterior to the rudimentary blind ending of the pulmonary artery. The aortic valve was well formed and measured 2.8 cm. in circumference. The coronary orifices were in their usual locations.

5. Atresia of the mitral valve. The mitral valve had failed to develop and there was no trace of leaflets or chordae with rudimentary musculature. There was no connection between the left atrium and the small left ventricle. The left atrium was almost completely divided by a longitudinal septum which was 0.2 cm. to 0.3 cm. in thickness. The division was not complete, however, and the two chambers were joined inferiorly. All pulmonary veins emptied into the medial chamber of the left atrium.

The left ventricle was completely independent of the pulmonary venous return. Its chamber was small, and its wall averaged 0.8 cm. in thickness.

Examination of the interatrial septum disclosed that the foramen ovale was sealed completely. The tricuspid valve measured 4.5 cm. in circumference. The leaflets were thin and smooth and the chordae tendinae were delicate, discrete strands.

A patent anastomosis was found between the aorta and the left pulmonary artery. The ascending aorta measured 1.3 cm. in diameter and appeared to be moderately dilated.

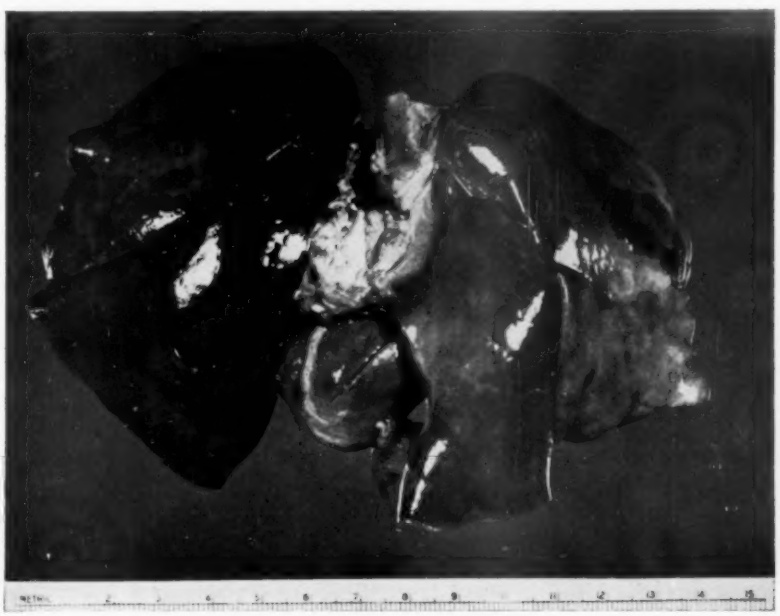

Fig. 3.—View of the lungs and heart from behind. Note the extreme congestion of the left lung as compared with the right.

The lungs were not weighed in order to preserve the relationship with the vascular system. All of the pulmonary veins opened into the left atrium. A careful search was made for anomalous drainage into the systemic venous system, such as was described by Edwards and DuShane,[3] but none was found grossly. The cut surface of the left lung was found to be congested, wet and dark reddish blue in color. Section of the right lung revealed less evidence of congestion, with some crepitation. Most of the smaller venous branches (1 to 2 mm.) of both lungs were found to be dilated, and they contained post-mortem thrombi. Microscopic examination of the lungs showed marked congestive changes of both arterial and venous systems. There was more dilatation of the arterial system on the left than on the right. There were no organizing thrombi.

Fig. 2.—Electrocardiographic tracings. There is evidence of right ventricular hypertrophy in the unipolar precordial leads. The appearance of the Q waves in the leads from the right side of the precordium is unusual in the tetralogy of Fallot.

The alveolar walls were thickened, and the alveoli contained large numbers of free cells, many of which were macrophages. These contained little or no pigment. The bronchi were empty, with normal epithelium.

Microscopic study of the hilar regions of both lungs showed dilatation of bronchial arteries and veins which undoubtedly served as the collateral bed which permitted blood to flow from systemic arteries into pulmonary arteries and from pulmonary veins into the tributaries of the vena cava.

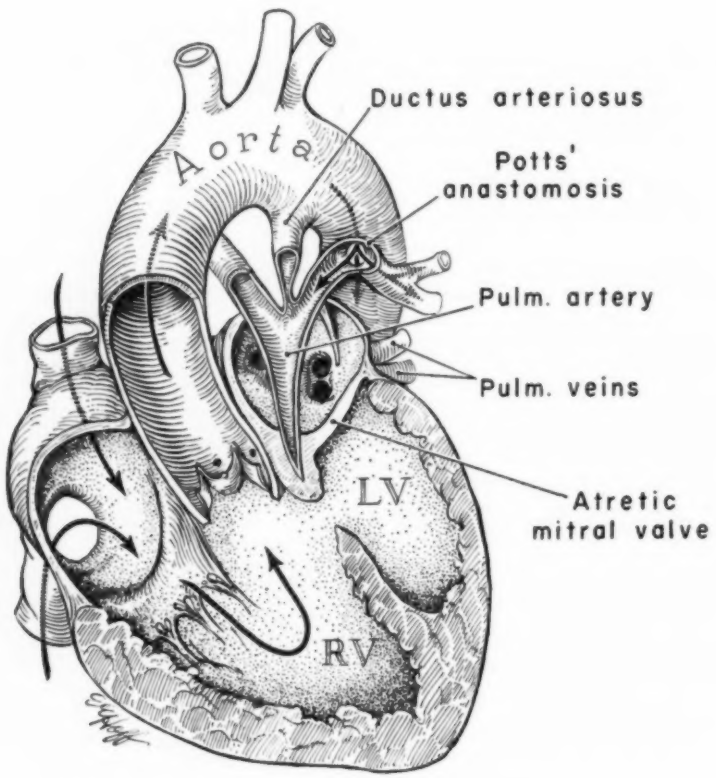

Fig. 4.—Diagram of the heart, illustrating mitral atresia, pulmonary atresia, and other anomalies.

DISCUSSION

The sequence of events following the creation of the aortico-pulmonary fistula is readily explainable in the light of the autopsy findings. Both afferent and efferent pulmonary blood flow had been through small collateral vessels which connected with systemic arteries and veins. The shunting of a relatively large amount of blood through the Pott's anastomosis into the lungs, especially the left, promptly resulted in pulmonary congestion. Theoretically, the creation of an interatrial defect at the time of the operation would have been desirable, since this would have provided a path of egress from the blind left auricle.

The pathway of pulmonary circulation before the operation appears to have been as follows: vena cava, right auricle, right ventricle, aorta, bronchial arteries, pulmonary arteries, pulmonary veins, and finally, small collateral veins leading into the vena cava, via the azygos system.

SUMMARY

A cyanotic infant of three months died following a Pott's operation (anastomosis between the aorta and the left pulmonary artery). Autopsy showed a hitherto undescribed anomalous structure of the heart. There was atresia of both the mitral and pulmonary valves, together with a questionably patent ductus arteriosus, intact interatrial septum, and an interventricular septal defect.

REFERENCES

1. (a) Abbott, Maude E.: Atlas of Congenital Cardiac Disease, New York, 1936, American Heart Association.
   (b) Bauer, D. DeF., and Astbury, E. C.: Congenital Cardiac Disease: Bibliography of the 1,000 Cases Analyzed in Maude Abbott's Atlas, AM. HEART J. **27**:688, 1944.
2. Taussig, Helen B.: Congenital Malformations of the Heart, London, 1947, The Commonwealth Fund.
3. Edwards, J. E., and DuShane, J. W.: Thoracic Venous Anomalies: 1. Vascular Connections of the Left Atrium and the Left Innominate Vein (Levo-atrio-cardinal Vein) Associated With Mitral Atresia in Premature Closure of the Foramen Ovale, Arch. Path. **49**:517, 1950.

ANNOUNCEMENTS

INTERNATIONAL SYMPOSIUM ON CARDIOVASCULAR REGULATIONS sponsored by the University of Vermont, College of Medicine, and the New Hampshire and Vermont Heart Associations will be held at Burlington, Vermont, Sept. 8, 9, 10, 1953. Papers will be presented by several speakers from abroad, such as: G. V. Anrep (Cairo, Egypt); E. Braun-Menéndez (Buenos Aires, Argentina); H. R. Croxatto (Santiago, Chile); O. Edholm (London, England); U. S. v. Euler (Stockholm, Sweden); W. Feldberg (London, England); H. Hensel (Heidelberg, Germany). Registration fee $2.00. For more information write to W. Raab, M.D., University of Vermont, College of Medicine, Burlington, Vermont.

A SYMPOSIUM ON CARDIOVASCULAR PHYSIOLOGY AND SURGERY will be presented by the University of Minnesota, under the auspices of the Minnesota Heart Association, from Sept. 14 to 16, 1953, in the Museum of Natural History Auditorium on the university campus. A host of internationally known physiologists and vascular surgeons will participate. The symposium will be open, without tuition fee, to all physicians and to qualified investigators in the field of cardiac physiology. Housing accommodations will be available on the campus for out-of-town registrants. Further information may be obtained from the Director, Department of Continuation Medical Education, University of Minnesota Hospitals, Minneapolis 14, Minn.

Book Reviews

MONOGRAPHS IN MEDICINE. Series I, Ed. by William B. Bean, M.D.; Associate Editors, Morton Hamburger, M.D., John A. Leutscher, Jr., M.D., and Stewart Wolf, M.D., Baltimore, 1952, Williams & Wilkins Company.

The stated purpose of this volume is to furnish a compromise between the journal focused on the temporary present and the fully comprehensive volume. It aims to provide a series of articles varying widely but in fields germane to general medicine. If successful, the editors apparently hope that the volume will be the first of a series. It is not unlike *Medicine* in its scope.

It contains the followlng articles: *Talking with the Patient*, Stewart Wolf; *Precordial Noises Heard at a Distance from the Chest*, William B. Bean; *Physiology of the Body Fluids*, William W. Wallace; *Angiocardiography*, Charles T. Dotter and Israel Steinberg; *Portal Hypertension*, Mary Ann Payne and Charles G. Child, III; *Pheochromocytoma*, Henry Aranow, Jr.; *Respiratory Failure in Neuromuscular Disorders*, Fred Plum; *Cortisone and ACTH in Infectious Processes*, Max Michael, Jr.; *Prevention of Rheumatic Fever*, Charles H. Rammelkamp, Jr. and Floyd W. Denny; *Amebiasis*, Henry E. Hamilton; *The Present Status of the Chemotherapy of Human Malaria*, L. H. Schmidt; *The Seasonal, Arthropod-borne, Virus Encephalitides*, R. Walter Schlesinger; *Sickle-Cell Anemia*, Byrd S. Leavell and William A. MacIlwaine; *The Growth and Maturation of the Erythrocyte*, Richard W. Vilter and John F. Mueller; *Chemical Agents Used in the Treatment of Inoperable and Far-advanced Neoplastic Disease*, David A. Karnofsky.

Both the names of the editors and those of the contributors guarantee the worth of the articles. They are beautifully written and several of them are of direct importance to the cardiologist. Others have a less direct appeal, such as the article on the growth and maturation of the erythrocyte and the one on the chemical agents used in the treatment of neoplastic disease. Nevertheless, they deal with fundamental aspects of cellular biology which will soon invade the field of cardiology and they may be read with profit by the cardiologist. Bean's article on precordial noises is a classic reminiscent of Osler, and the articles on angiography and on portal hypertension are also beautiful and complete.

This volume should be on the shelves of every good medical library.

One point which puzzled the reviewer was the price ($12.00) which may militate against the book's getting a very wide circulation. This method of collecting a series of articles within one volume is in sharp competition with the technique which other American and British publishers have adopted of publishing short monographs as small, separate, moderately priced volumes. The medical book trade is sure to follow these experiments closely. However, there is no question of the value of the review-monograph in orienting the medical reader in the vast profusion of medical literature which is flooding the country.

J.J.

PROCEEDINGS OF THE ANNUAL MEETING, COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH, AMERICAN HEART ASSOCIATION, 1952. New York, 1952, American Heart Association. 113 pp.; pr. $1.75.

The scientific section of the *Proceedings* contains six papers, five of which deal with various aspects of atherosclerosis from the experimental point of view. The subjects discussed include isotopic studies of cholesterol metabolism, the relation between plasma lipoprotein concentration and the susceptibility of different species to atherosclerosis, the mechanism of the clearing action of heparin on lipemic serum, the inhibition of experimental atherosclerosis by estrogens, and a method for studying the early stages of cholesterol atherosclerosis by microscopic examination of the intimal surface of the rabbit's aorta. The sixth paper deals with the production of acute arterial injury in dogs by injections of epinephrine or allylamine and saline suspensions of egg yolk.

The second section is devoted to a series of brief nontechnical reports on recent advances in various fields of cardiovascular research, including atherosclerosis, coronary thrombosis, hypertension, rheumatic heart disease, congenital heart disease, and cardiac surgery.

K.E.